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EFFECT OF ACUPUNCTURE AS COMPLEMENTARY THERAPY IN PATIENTS WITH ESSENTIAL HYPERTENSION- A CLINICAL RESEARCH PROTOCOL

Dissertação de Candidatura ao grau de Mestre em Medicina Tradicional Chinesa submetida ao Instituto de Ciências Biomédicas de Abel Salazar da Universidade do Porto.

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DEDICATION

To my parents Lea and Mauro for their love.

To Alexandre, Isabella and Gabriella my greatest gifts in life.

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RESUMO

Introdução: A hipertensão arterial é a principal causa de mortalidade na população em geral. Ela é um importante fator de risco para doença vascular cerebral, principal causa de morte de um adulto e de incapacitância em muitos países desenvolvidos. A sua prevalência é estimada em cerca de um bilião de pessoas e pode estar relacionada com até 7 milhões de morte por ano. Em Portugal estima-se que cerca de 42% da população adulta (três milhões) de pessoas sejam hipertensos. Muitos deles não conhecem a sua situação e apenas 11% destes são tratados adequadamente. A prevalência de hipertensão aumenta com a idade e atinge cerca de 78% entre as pessoas com mais de 64 anos, o que motiva um maior número de consultas médicas, gerando altos custos para o sistema nacional de saúde. Segundo a literatura, o primeiro ano de tratamento 40% irão abandonar a terapia e após 5-10 anos até 60% irão interromper o uso da sua prescrição para hipertensão. O uso da acupuntura poderá ajudar a superar estas dificuldades ao diminuir ou substituir a quantidade de droga necessária e também porque as visitas frequentes à clínica melhoram a aderência ao tratamento (medicamentos e/ou mudanças no estilo de vida).

Objetivo: Estudar o efeito agudo da acupuntura nos pacientes com hipertensão arterial essencial utilizando o monitoramento de pressão arterial de 24 horas. (MAPA).

Métodos: Um protocolo clínico preliminar, prospectivo, randomizado, controlado, duplo-cego. Pacientes com idade inferior a 70 anos, com hipertensão essencial classificada com normal alta, grau1 ou grau 2 de acordo com as recomendações da ESH/ESC serão avaliados com um MAPA inicial (basal) e a análise do risco cardiovascular será realizada. Eles serão então randomizados para acupuntura 'verdadeira' ou acupuntura sham- a acupuntura verdadeira será os pontos selecionados como úteis no contexto da medicina tradicional chinesa, no caso deste estudo: **F39, Pc 6, Rg14, F20, Rs12, L6, R7** e acupunctura sham aqueles pontos considerados sem ação para hipertensão orientada por artigo previamente publicado. Os pacientes serão submetidos a 3 sessões (Terça, quarta e quinta) de terapia acupuntura (verdadeira ou sham). A tensão arterial e a frequência cardíaca serão mensuradas de acordo com os critérios da ESH/ESC antes e após cada intervenção. Um outro MAPA será realizado após o término das

3 sessões. O principal parâmetro será a média das pressões arteriais sistólica e diastólica. Paramêtros secundários serão as médias das tensões arteriais sistólica e diastólica durante o dia e durante a noite, e também a variabilidade das tensões arteriais (standard deviation em torno do valor médio).

Resultados: Dois grandes contribuintes para a hipertensão arterial são o sistema renina-angiotensina-aldosterona e a ativação crónica do sistema nervoso simpático. Alguns estudos experimentais recentes relataram que a acupuntura reduz a atividade neural no rVLM, com isso reduzindo a atividade simpática. Há também trabalhos dizendo que a acupuntura pode reduzir os níveis plasmáticos de renina-angiotensina-aldosterona. Deste modo, este estudo pode revelar um decréscimo significantivo nos níveis de tensão arterial. Também como um parâmetro secundário, a variabilidade da tensão arterial pode ter um valor prognóstico no tratamento da hipertensão , ao analisar este parâmetro poderemos avaliar também, indiretamente, o efeito da acupuntura na piora das lesões de órgão alvo da hipertensão e incidência de eventos cardiovasculares.

Discussão: Resultados deste estudo podem auxiliar um maior estudo , prospectivo, randomizado, multi-cego, com follow up mais prolongados e indicar a possibilidade de termos uma outra ferramenta interessante para tratar esta doença que é responsável por um grande número de incapacitados e também mortes ao redor do mundo.

Palavras-chave: Hipertensão, acupuntura, medicina tradicional chinesa

ABSTRACT:

Introduction: Hypertension is the first cause of death worldwide. It is also an important risk factor for cerebral vascular disease, main cause of adult death and disability in many developed countries. Hypertension prevalence in the world is estimated to be almost 1 billion individuals and it can be related to as much as 7million deaths per year. It is estimated that in Portugal about 42% of the adult population(3million people) have hypertension. Many of them unaware of their condition, and only about 11% are treated adequately. The prevalence of hypertension increases with the age of the people, reaching about 78% among older than 64 years and motivates more clinical consultation, generating high costs to the National Health System. According to the literature, in the first year of therapy 40% will abandon the treatment and after 5-10 years as much as 60% will interrupt their prescription for hypertension. The use of acupuncture could help overcome these difficulties, by either diminishing or substituting the amount of drug required, and also because frequent visits to the clinic eases the compliance to the treatment (drugs and/or adjustment of lifestyle).

Objective: Study the acute effect of the acupuncture in patients with essential hypertension using 24 –Ambulatory Blood pressure monitor results.

Methods: A clinical protocol of preliminary, prospective, randomized, controlled, double-blinded clinical trial design. Patients aged < 70 years, with essential hypertension classified as high normal, grade1 or grade 2 hypertensive patients according to ESH/ESC 2007 guidelines will be evaluated with an initial (baseline) 24-ABPM and assessment of cardiovascular risk will be made. Then they will be randomized to either 'real' acupuncture or sham acupuncture. -'real' acupuncture being points selected as useful in the context of Chinese medicine-in this study **F39, Pc 6, Rg14, F20, Rs12, L6, R7** and sham acupuncture those points considered inactive for hypertension, oriented by previous published trial. The patients will be submitted to 3 sessions (Tue.Wed,Thur) of acupuncture treatment (real or sham). BP and heart rate will be measured according to ESH/ESC criteria before and after each intervention. Another 24-ABPM will be made after the completion of the 3 sessions. Main parameter will be the average systolic and diastolic blood pressure. Secondary parameters will be average daytime and nighttimes systolic and diastolic blood pressure, and also the blood pressure variability (standard deviation around mean values).The acute effect of the blinded acupuncture will be done on the first day of treatment.

Results: Acupuncture exerts sympatholytic, pro-vagotonic, and action on the renin, angiotensin aldosterone system effects according to recent literature. It was discovered a specific neurological pathway participating in acupuncture inhibition of excitatory cardiovascular reflexes at the rostral ventrolateral medulla cardiovascular center . All of which acts in the pathophysiology of the hypertension .The study may reveal a significant decrease in both systolic and diastolic blood pressure, compared to the sham group. By analysing the 24-ABPM data we could get more accurate, reproducible measurement of the extent of the reduction induced by the treatment, in addition, it can provide information regarding to in which part of the 24 hours (day or night) the results were more pronounced.

Discussion: Results from this study may in the future grant a larger prospective, controlled, multi-blinded, randomized protocols, with longer follow up periods, to have another interesting tool to treat this awful disease, responsible for a great number of disabilities and deaths worldwide.

Key words: Hypertension; acupuncture; traditional Chinese medicine

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List of abbreviations

ABPM- Ambulatory Blood Pressure Monitoring

AT1- angiotensin II type 1 receptor

AT2- angiotensin II type 2 receptor

ACC -American College of Cardiology

ACE -angiotensin conversor enzyme)

ACE (angiotensin conversor enzyme)

AHA -American Heart Association

ALT- Algor Laedens Theory

BP-blood Pressure

C- cardial conduit ("heart")

CHD-coronary heart disease

CHF-congestive heart failure

CNS- central nervous system

CO- Cardiac Output

CVD-Cardiovascular Disease

DA- Dopamine

DBP- Diastolic Blood pressure

DGTCM-German Society of Traditional Chinese Medicine

DPN Deep Peroneal Nerve

EA- Electro acupuncture

ECG Eletrocardiogram

EDCF-endothelium derived contraction factors

EDRF Endothelium Derived Relaxation Factor

EP-epinephrine

eNOS -endothelial nitric oxide synthetase

EHT- Essential Hypertension

ESC -European Society of Cardiology

ESH -European Society of Hypertension

Ex-HN-Extra point head and neck

F- Felleal conduit ("gallbladder")

GABA ∂aminobutiric Acid

GC- Guiding Criteria

H+ - hydrogen ion

H- hepatic conduit ("liver")

HT-hypertension

HD –Heidelberg

HF-Heart Failure

HR heart rate

ICBAS-Instituto de Ciências Biomédicas Abel Salazar

INCOR-Instituto do Coração

It- Tenuintestinal conduit

IC –intestini crassi conduit

K+ - potassium ion

L- Lienal conduit ("spleen")

LV left ventricle

MA-Manual Acupuncture

MAPA- Monitoramento de Pressão Arterial Ambulatorial

Na- sodium

NaCl- sodium chloride

NE- Norepinephrine

NIH – National Institute of Health

NO- nitric oxide

nNOS neuronal nitric oxide synthetase

NR: nuclei raphe

NRP-medullary nucleus raphé pallidus

P- pulmonar conduit (“lung”)

PAG- periaqueduct gray

PR- Peripheral resistance

Pc- Pericardial conduit

Pc6-Pericardium 6

R – renal conduit (“kidney”)

Rg- Regens sinartery (“governing vessel- dumo)

Rs –Respondens sinartery (“controlling vessel”- renmo)

rVLM-rostral ventral lateral medulla

S –stomach conduit

SBP- Systolic Blood Pressure

SHR-Spontaneous Hypertensice Rat

TCM-Traditional Chinese Medicine

Tk- tricaloric conduit

UP-Universidade do Porto

USP-Universidade de São Paulo

V- Vesical conduit (“bladder”)

vlPAG: ventrolateral periaqueductal gray

WHO- World Health Organization

WKS-Winstar-Kyoto Rat

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1. INTRODUCTION

1.1Epidemiology

Hypertension is the first cause of death worldwide not only due to its high prevalence among the population but also because it is the major risk factor for many cardiovascular and related diseases, and can also lead to other diseases that increase the cardiovascular risk as well. (Ezzati, Lopez, Rodgers, Vander Hoorn, Murray, & Group., 2002)(Kearney, Whelton, Reynolds, Muntner, Whelton, & He, 2005)(Martiniuk AL, 2007) As such it is also an important risk factor for cerebral vascular disease, main cause of adult death and disability in many developed countries.(Flachskampf, et al., 2007). Hypertension is also associated with an increase in the risk of dementia.(Skoog, et al., 1996)

Hypertension prevalence worldwide is estimated to be almost 1 billion individuals and it can be related to as much as 7million deaths per year.(WHO, 2002)

It is also estimated that in Portugal around 42% of the adult population aged 18-90 years has hypertension. That number corresponds to approximately 3 million people. Among those patients only 36% are aware of their high blood pressure and only about 11% are treated adequately. The prevalence of hypertension increases with the age of the people, reaching about 78% among older than 64 years(Macedo, Lima, Silva, Alcantara, Ramalhinho, & Carmona, 2005), and motivates more clinical consultation, generating higher costs to the national health system.(Zurro & Pérez, 2008)

There are some racial differences in the incidence of hypertension, both environmental and genetic factors may contribute to this factor. Migrants tend to develop the rates of hypertension similar to the new resident zone and studies with before the age of 55 high blood pressure occurs almost 4 times more frequently among those with family history of high blood pressure (BP). But for most individuals the hypertension is probably a multigenic disorder and the environment seems to play a big role in its development. Essential hypertension is a polygenic thus different patients may carry different phenotypes (obesity, dyslipidaemia, insulin resistance) depending on the different subset of genes involved (Fauci, et al., 2008)

Among the environmental factors are obesity and weight gain, dietary sodium intake, low intake of calcium and potassium, alcohol consumption, psychosocial stress, low levels of physical activity and others.(Fauci, et al., 2008)

1.2 Pathophysiology of Hypertension

$$BP = CO \times PR$$

Equation 1- Blood Pressure

Where: BP= blood pressure CO= Cardiac Output PR= Peripheral Resistance

And:

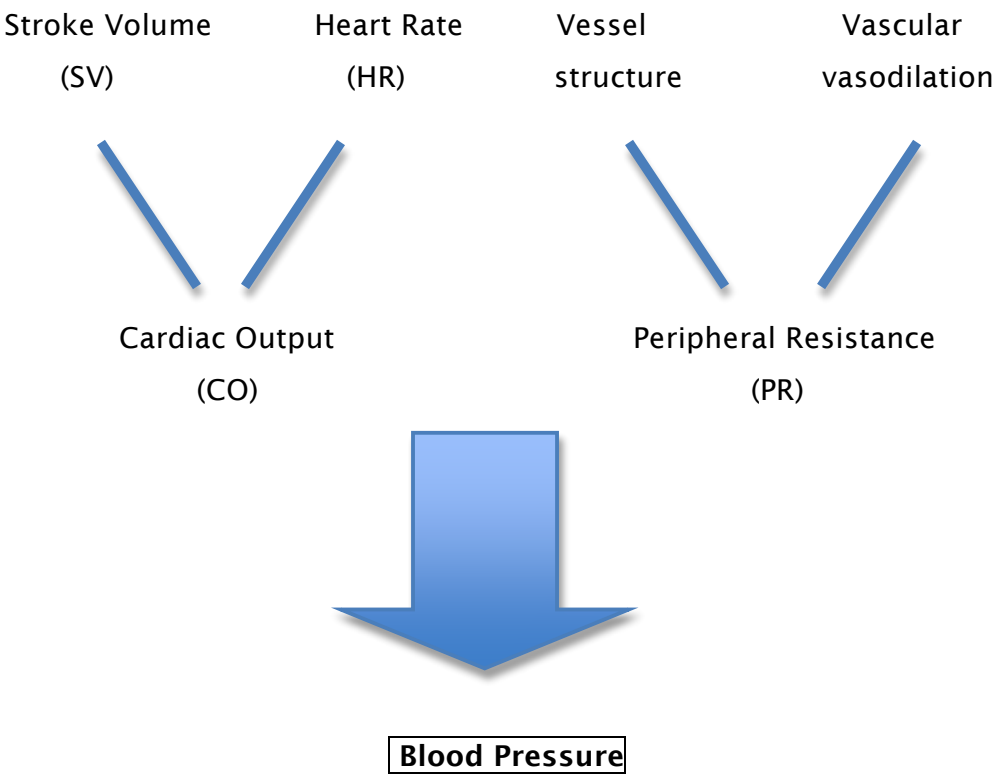


Figure 1- Components of Blood Pressure

Mechanisms to increase BP:

- Increase in SV
- Increase in HR
- Increase pressure on vascular structure
- Alteration in vascular function

1.2.1 Intravascular Volume

The increase in BP is related to sodium linked to choride but not to the sodium without the cholide. Increase in NaCl intake and/or decreased capacity of excretion leads to an increase in the intravascular volume thus increasing the cardiac output. Over time there is an adaptation with increase in vascular resistance, releasing of natriuretic peptide (that augment the renal sodium excretion) , high BP leads to a higher glomerular filtration rate , decreasing the absorbing in the renal tubules, thus increasing sodium excretion, all these making the CO normal again. When an impaired capacity of Na excretion exists, higher BP are required to induce natriuresis and reach sodium balance.

Increased neural activity to the kidney elevates renal tubular reabsorption of sodium. The higher concentration in plasma sodium in its turn may also lead to an increase in BP to try to augment the glomerular filtration rate in order to balance the sodium, thus making a vicious cycle.

Also some organs (brain, kidney) have an autoregulation of flow,i.e. they keep the flow to the organ steady, even when the intravascular volume is augmented. They manage to do it by increasing the resistance of the afferent arteries, but then this resistance is transmitted to the other vessels and leads to a higher BP.

1.2.2 Autonomic Nervous System

Short term BP are modulated by adrenergic reflexes while long term regulation are regarded as derived from adrenergic function (hormonal, volume factors).

Cardiovascular homeostasis are maintained due to pressure, volume and chemoreceptors. Norepinephrine (NE), epinephrine (EP) and dopamine (DA) are the endogenous cathecolamines and all of them are important in this process and they have different affinities to different receptors, but also the receptors has different functions. Thus, it is important to understand it in order to comprehend the action of different anti-hypertensive drugs.

Norepinephrine has greater affinity to α receptors:

α 1 receptors are in the smooth muscle and elicits vasoconstriction

α 2 receptors are a negative feedback to NE release, ie inhibits the NE release when linked to NE

Epinephrine has better affinity to ß receptors

ß 1 receptors stimulates increase in HR and strengthens the cardiac contraction, increasing CO, also this receptor increases the rennin release from the kidney

ß 2 receptors relaxes the smooth muscle and leads to a vasodilation

Also there is a downregulation of receptors when there is higher concentration of circulating catecholamines (the more catecholamine, the lower number of receptors and vice versa)

The reflex action on the blood pressure regulation occurs on a minute-to-minute basis. There are baroceptors in the carotid sinuses and in aortic arch. So when the BP increases, there is an increase in these receptors firings leading to a decrease in the sympathetic outflow resulting in decreases in BP and HR. This effect is quite rapid and is the main responsible for the adjustment of the BP during postural changes, stress and changes in blood volume such as in a hemorrhage. But also this reflex is susceptible to adaptations, so in hypertensive patients this receptors tend to respond to higher BP levels.

1.2.3 Renin-Angiotensin-Aldosterone (see Figure 2)

Renin is a substance that is produced in the segment of justaglomerular cells –in the segment of the renal afferent arteriole and in the macula densa close to the distal loop of Henle. There are 3 main stimuli to renin release:

1. Decrease in NaCl transport in the loop of Henle-also indicating low BP (sodium balance mechanism)
2. Decrease pressure or decreased strech in the renal afferent arteriole (baroceptor)indicating low pressure and needs to elevate BP
3. Sympathetic nervous stimulation via ß 1 receptors

And the release is inhibited by the opposite of the situations above.

Renin activates the angiotensinogen to form angitensin I. An angiotensin converting enzyme (ACE) will , mainly in the pulmonary circulation, convert the angiotensin I in angiotensin II. This ACE also inactivates another vasodilator, the bradykinin.

Angiotensin II has important role in hypertension due to many mechanisms:

- Acts primarily via angiotensin II type 1 receptor (AT1), leading to aldosterone secretion by the adrenal mucosa. Aldosterone is a mineralocorticoid that acts in the sodium reabsorption on the renal cortical collecting duct. It acts in the Na+/H+K+, increasing sodium reabsorption eliminating H+ and K+ resulting in hipocalemia and alkalosis. Moreover aldosterone also is a potent mitogen stimulating vascular smooth-muscle cell and myocyte growth.And it can also participate in the cardiac hypertrophy and congestive heart failure, independent of its action increasing the blood pressure.
- May also play a role in the pathogenesis of atherosclerosis through a direct action on the vessel wall. And can cause vasoconstriction.
  Whereas angiotensin II receptor type 2 has the opposite effects, such as vasodilation, Na excretion and inhibition of cell growth and matrix formation and improves remodelling by stimulating vascular smooth cells apoptosis and contributes to the regulation of the glomerular filtration rate. Blockade of AT1 ellicits AT2 activity.

The renin-angiotensin-aldosterone axis is not always the villain, when there is a situation of volume contraction or reduced NaCl intake, the homeostasis of the BP are achieved via this axis.

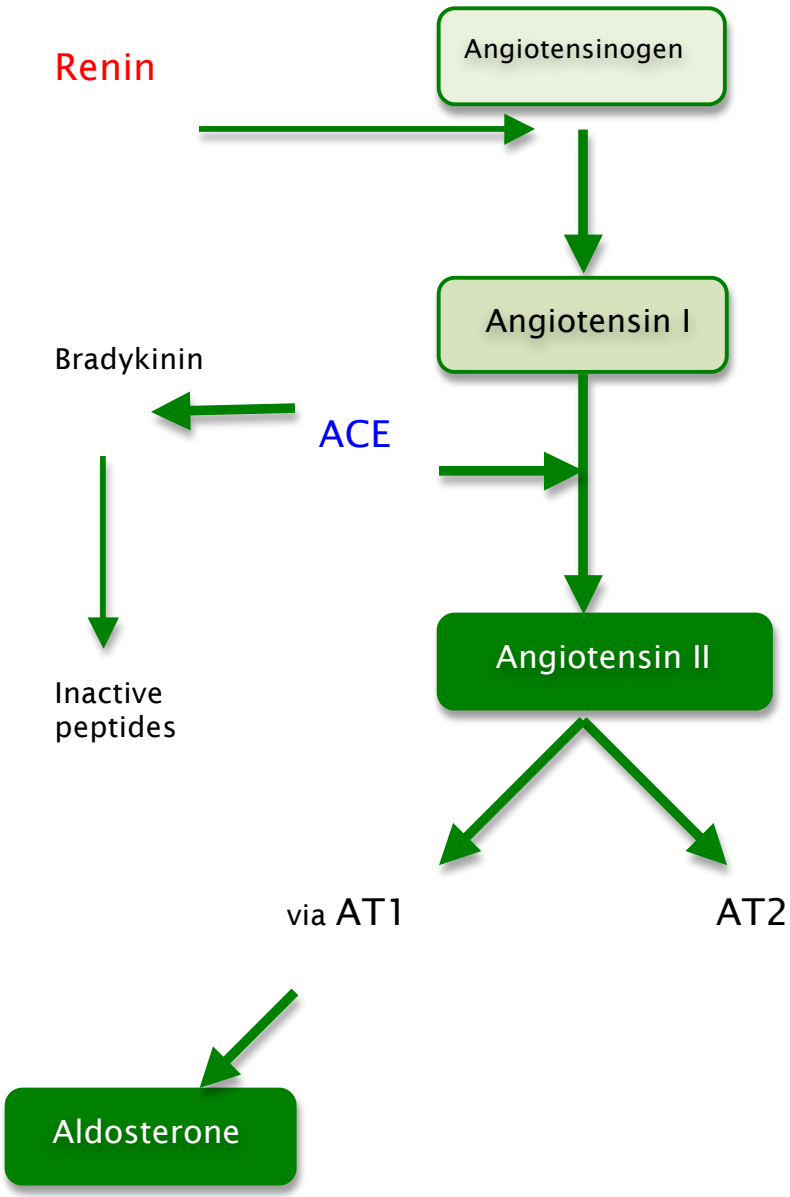


Figure 2- Renin-Angiotensin-Aldosterone axis

1.2.4 Vascular mechanisms

Vascular compliance and the diameter are important determinants of BP and even small changes in vascular diameters leads to a significantly increase resistance.

In hypertension there is structural, mechanical and functional changes that may reduce the lumen diameter in the arteries and arterioles.

The lumen diameter also is dependent on the elasticity of the vessel- the higher the elasticity the higher the compliance, i.e. vessels with high elasticity

can take an increase in blood volume without changing very much the pressure. Hypertensive patients usually have arteriosclerosis making the arteries stiffer, and the stiffness of the arteries has a predictive value for cardiovascular events.

The alterations in the vascular tone and vascular growth, modulated by intracellular pH, in hypertensive patients can be explained by :

1. Increased Na leads to a increase in intracellular calcium (by action in the permeability), increasing the vascular tone
2. Alterations in pH caused by the Na+/H+ pump leads to a greater sensibility to calcium by contractile apparatus, also the activity in this pump also increase the sensitivity to mitogens, thus stimulating the smooth muscle cell growth.

The vascular tone also is dependent on many vasoactive substance produced by the endothelial cells, such as the nitric oxide (NO) , a potent vasodilator. In hypertension this endothelium dependant vasodilation is impaired.

It is not known yet if these vascular abnormalities in hypertensive patients are primary or secondary to increased arterial BP, but weight loss, aerobic exercise and anti-hypertensive medicaments can improve them.

1.3 Target Organs in Hypertension

Hypertensive patients is at greater risk to all artheriosclerosis manifestations. And hypertension is an independent risk for heart failure, coronary artery disease, stroke, renal disease and peripheral artery disease.

1.3.1 Heart

Compromise of this organ is the principal cause of death among hypertensive population.

Heart disease in hypertension is due to both structural and functional adaptations leading to left ventricular (LV) hypertrophy, diastolic dysfunction, congestive heart failure (CHF), atherosclerotic coronary disease , microvascular disease and cardiac arrhythmias.

Patients with LV hypertrophy have an elevated risk for coronary heart disease (CHD), CHF, stroke and sudden death. Adequate control can revert this process by reducing the LV hypertrophy.

1.3.2 Brain

Hypertensive patients have an increased risk to have stoke either by brain infarction (85%) or hemorrhage - intracerebral or subarachnoid -(15 %). And the incidence is proportional to the level of BP, particularly the systolic BP among those older than 65 years. Lowering the level of BP decreases the risk for stroke.

Another burden of hypertension is the impairment of cognition in aging population may be due to either strategic localized infarct or multiple lacunar (subcortical white matter) infarction. Studies are investigating the extent of the benefit of treating hypertension for prevention of dementia.

In malignant hypertension, failure in autoregulation of brain flow may lead to encephalopathy with severe headache, nausea and vomiting and constitute an emergency situation as it can progress to stupor, coma, seizures and death within hours.

1.3.3 Kidney

Hypertension is a risk factor for renal damage and can lead to end stage renal disease (ESRD), and here also the risk is proportional to the increase in BP levels above optimal, and also has racial differences, being the black men at higher risk than white men at the same BP level.

Microalbuminuria (urine albumin/creatine ratio 30- 300mg/g) and also macroalbuminuria (urine albumin/creatine ratio >300mg/g) are early markers for kidney injury and are risk factoer for progression of the disease.

1.3.4 Peripheral arteries

Alterations in structure and/or function of the arteries are part of the pathogenesis of hypertension, but to make matters worse, blood vessels can be also a target for damages by long term elevated BP leading to a vicious cycle. Those patients with lesion in arteries of the legs has greater risk of CVD.

1.4 Diagnosis of Hypertension

Diagnosis of Hypertension should:

1) Establish the blood pressure levels- as the level of blood pressure is not constant , the diagnosis should be based on multiple blood pressure measurements, taken in different occasions over a period of time. Nevertheless if the patient has a marked high blood pressure, has a high or very high cardiovascular risk profile, signs of damage in hypertension related organ, then the revaluation should be done in a shorter period (weeks or days)(ESH/ESC, 2007)

2) Identify secondary causes of hypertension (as related above)

3) Assessment of overall cardiovascular risk factors, target organ damage and concomitant diseases (blood pressure level, diabetes mellitus, metabolic syndrome, one or more of the following subclinical organ damages: ECG with strain pattern; ecocardiographic (concentric) left ventricular (LV) hypertrophy; ultrasound with evidence of thickening of carotid artery wall or plaque; increased arterial stiffness; moderate increase in serum creatinine clearance; microalbuminuria or proteinuria or with cardiovascular or renal disease.

1.4.1 Recommendations when measuring the blood pressure:

Box 2 Blood pressure (BP) measurement

When measuring BP, care should be taken to:

- Allow the patients to sit for several minutes in a quiet room before beginning BP measurements
- Take at least two measurements spaced by 1–2 minutes, and additional measurements if the first two are quite different
- Use a standard bladder (12–13 cm long and 35 cm wide) but have a larger and a smaller bladder available for fat and thin arms, respectively. Use the smaller bladder in children
- Have the cuff at the heart level, whatever the position of the patient
- Use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic BP, respectively
- Measure BP in both arms at first visit to detect possible differences due to peripheral vascular disease. In this instance, take the higher value as the reference one
- Measure BP 1 and 5 min after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which postural hypotension may be frequent or suspected
- Measure heart rate by pulse palpation (at least 30 sec) after the second measurement in the sitting position

Figure 3- Recommendations for Blood Pressure Measurement

From:(ESH/ESC, 2007)

1.4.2 Ambulatory blood pressure

Provides information on 24-hour average blood pressure as well as on mean values over more restricted periods such as the day, night or morning. The physician should not substitute the conventional BP measure but some reports showed that office taken BP has limited relation with the 24-hour average(Mancia, et al., Twenty-four hour ambulatory blood pressure in the Hypertension Optimal Treatment (HOT)study, 2001)(Mancia, Omboni, Ravogli, Parati, & Zanchetti, 1995)(Mancia, et al., 2007).

Some advantages of 24-ABPM over office only measure:

-It has a higher reproducibility over time(Coats, Radaelli, Clark, Conway, & Sleight, 1992)(Mancia, Ulian, Parati, & Trazzi, 1994)

-Absent or insignificant 'white coat' and placebo effect(Staessen, et al., 1994)(Mancia, Omboni, Parati, Ravogli, Vilani, & Zanchetti, Lack of placebo effect on ambulatory blood pressure, 1995)

-Better prognostic value(ESH/ESC, 2007)

-Gives information on blood pressure variability- (standard deviation around mean values), the variability of blood pressure may have a

prognostic value in hypertension treatments. (Mancia, et al., 2007)(Mancia, Prognostic value of long-term blood pressure variability:the evidence is growing, 2011)

1.5 Classification of Hypertension

1.5.1 According to BP levels

According to the 2003 and 2009 ESH (European Society of Hypertension)/ESC (European Society of Cardiology) the blood pressure is classified as this table shows:

Table 1 Definitions and classification of blood pressure (BP) levels (mmHg)

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Isolated systolic hypertension should be graded (1, 2,3) according to systolic blood pressure values in the ranges indicated, provided that diastolic values are <90 mmHg. Grades 1, 2 and 3 correspond to classification in mild, moderate and severe hypertension, respectively. These terms have been now omitted to avoid confusion with quantification of total cardiovascular risk.

Table 1-Classification of Hypertension (ESH/ESC 2007)

(ESH/ESC, 2007)

Also there are some points to be considered when classifying the blood pressure level:

-When systolic blood pressure (SBP) and diastolic blood pressure (DBP) are in different categories, always consider the higher category for all purposes

-Isolated systolic blood pressure should be graded according to the same systolic blood pressure value indicated for systolic-diastolic hypertension,

however the association with low diastolic blood pressure (60-70mmHg) should be regarded as an additional risk

-Threshold for hypertension should be considered based on the level and profile of total cardiovascular risk.(ESH/ESC, 2007)

Moreover, different from the previous recommendations, the ESH/ESC now states that the blood pressure should not be evaluated as an isolate factor but in relationship to their total cardiovascular risk, i.e. associated concomitantly with metabolic risk factors because the risk to end organ damage and disease is greater than the sum of the individual components, this may occur because obesity, particularly abdominal obesity is very frequently associated with hypertension, dyslipidaemia and insulin resistance. The constellation of hypertension, dyslipidaemia and insulin resistance is the metabolic syndrome. Insulin resistance is also linked to an alteration in endothelium, dysbalancing the production of mediators that regulate platelet aggregation, coagulation and fibrinolysis and vessel tone. So when these risk factors cluster its potentiates the risk for CHD, stroke, diabetes making the mortality due to CVD even higher.

Table 2-Stratification of Cardiovascular Risk

Blood pressure (mmHg)					
Other risk factors, OD or Disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP≥180 or DBP≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

" Stratification of CV Risk in four categories. SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: cardiovascular; HT: hypertension. Low, moderate, high and very high risks refer to 10-year risk of a CV fatal or non-fatal event. The term 'added' indicates that in all categories risk is greater than average. OD: subclinical organ damage; MS: metabolic syndrome. The dashed line indicates how definition of hypertension may be variable, depending on the level of total CV risk. "

(European Heart Journal (2007) 28, 1462–1536 doi:10.1093/eurheartj/ehm236)

1.5.2 According to aetiology

Essential or Primary Hypertension is when there is no identifiable cause (80-95% of the cases) or Secondary Hypertension when it is secondary to another pathology such as:

- Renal disease (parenchymal diseases, renal cysts, polycystic renal disease, renal tumours)
- Genetic causes, Reno vascular hypertension (atherosclerotic, fibro muscular dysplasia)
- adrenal (primary hyperaldosteronism, Cushing's syndrome, 17α hydrolase deficiency, 11ß hydrolase deficiency, 11-hydroxysteroid dehydrogenase deficiency-liquorice, pheocromocytoma)
- Aorta coarctation
- Obstructive sleep apnoea
- Associated with pregnancy (eclampsia, preeclampsia)
- Neurogenic (psychogenic, diencephalic syndrome, familial dysautonoma, polyneuritis –acute porphyria, lead poisoning-, acute increased intracranial pressure, acute spinal cord section)
- Endocrine (Hypothyroidism, hyperthyroidism, hypercalemia, acromegaly)
- medications (high dose estrogens, adrenal steroids, decongestants, appetite suppressants, cyclosporine, tricyclic antidepressants, monoamine oxidase inhibitors, erythropoietin, nonsteroidal anti-inflammatory agents, cocaine)

The essential hypertension is the most common form of hypertension, occurring in general after the 4th decade of life, and its actual cause is unknown, and a multifactorial hypothesis is probable. Many unknown factors interact to lead to an increase in total peripheral resistance due to a change in the arterioles, thus leading to an elevation of diastolic pressure that leads to an increase also in systolic pressure in response to a pressor stimulus. When there is decrease compliance in the arteries, there is an increase in systolic pressure and decrease in diastolic pressure (as we see in some elderly patients in the isolated systolic hypertension)(Randal, 1991). Before the structure of the arterioles and/or arteries changes there is a functional alteration and the vasoconstriction can due to an excessive production or low decrease in 'hypertensive' factors such as rennin/angiotensin/aldosterone, vasopressin, endotelin, sympathetic nervous system-adrenalin, norepinephrine.

1.5 Conventional Therapy of Hypertension (ESH/ESC, 2007):

As seen above, the therapy of hypertension has to consider not only the blood pressure levels but also the patient age, associated morbidities (diabetes mellitus, renal disease, coronary artery disease, end organs damage etc.), thus accessing the overall cardiovascular risk. An observational study of more than 1 million subjects indicated that death from both coronary heart disease and stroke increases linearly with the blood pressure levels.(Lewington, Clarke, Qizilbash, Peto, & Collins, 2002)

Table 3-Recommended Conventional therapy for Hypertension

	Blood pressure (mmHg)				
Other risk factors OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP≥180 or DBP≥110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
1–2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + Immediate drug treatment
≥3 risk factors, MS or OD	Lifestyle changes	Lifestyle changes and consider drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Drug treatment	Lifestyle changes + Immediate drug treatment
Diabetes	Lifestyle changes	Lifestyle changes + Drug treatment			
Established CV or renal disease	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment	Lifestyle changes + Immediate drug treatment

(ESH/ESC, 2007)

Lifestyle change includes smoking cessation, weight reduction (and stabilization), reduction in alcohol and salt intake, physical exercise, increase in fruit and vegetable consumption, decrease in saturated and total fat intake, periodically reinforced recommendations, close follow up.

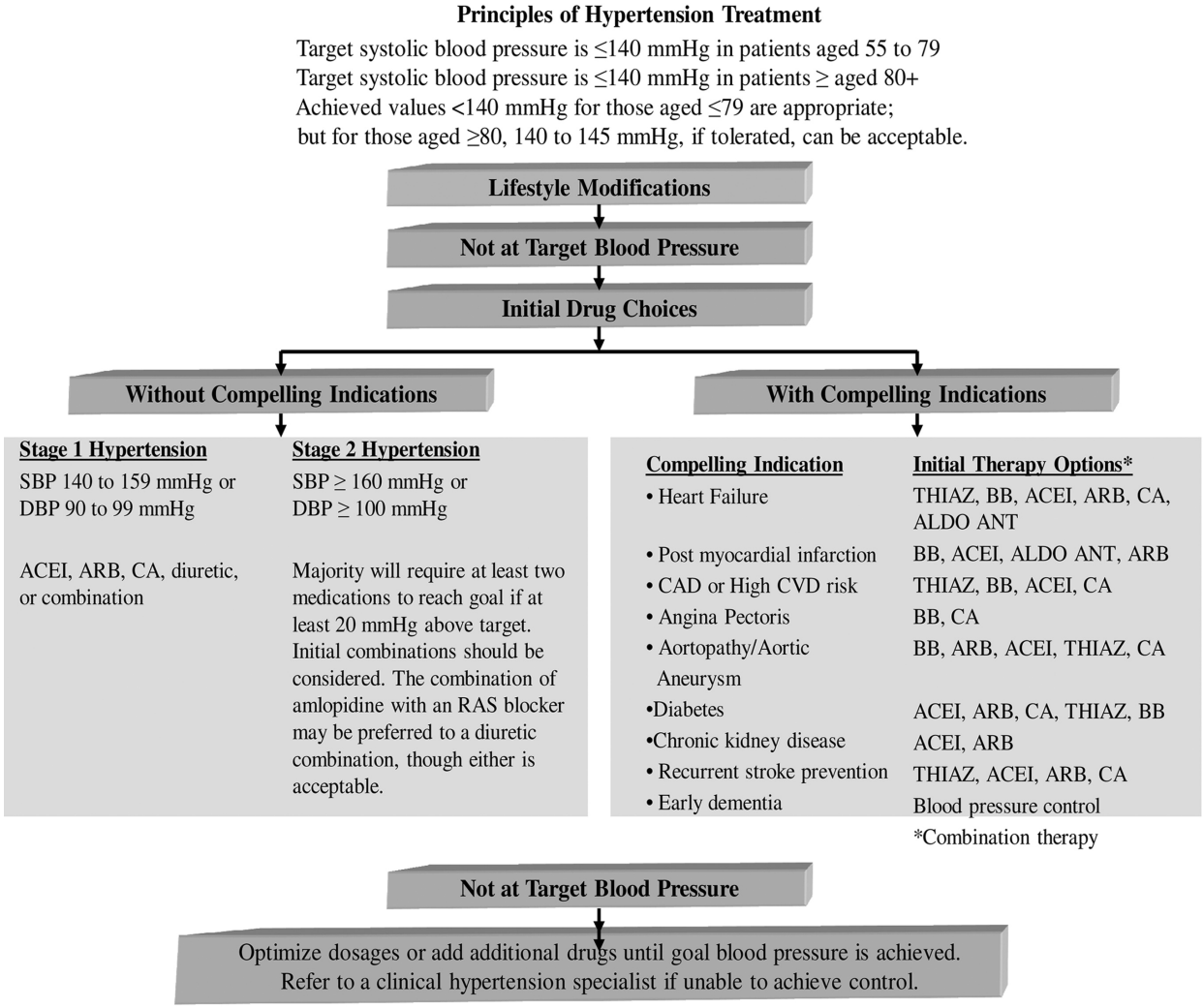
An important message from the newest ESH/ESC Guidelines 2011 is that the management of individual components of cardiovascular risk such as smoking, diet, exercise, blood pressure and lipids have impacts on the total risk, than if the control of one of them is not optimal (i.e. hypertension in the elderly) the total risk can still be reduced by reducing other risk factors such as smoking or lipids. (ESH/ESC, 2011)

There are five main classes of drugs to be used, alone or in combination, **always aiming to lower the BP**: Thiazide diuretics, calcium antagonists, ACE (angiotensin conversor enzyme) inhibitors, angiotensin receptor antagonists and ß-blockers. In patients with diabetes or metabolic syndrome ß-blockers especially with thyazide diuretic should be avoided. The drug choice should be made taking into account the compliance (once a day is better than 3 times a day), side effects, and there are some pathologies that have some preferred drugs to be used as antihypertensive.

According to ESH/ESC the therapy in hypertension aims to achieve maximum reduction in long term total cardiovascular disease risk, treating not only the blood pressure but all others reversible factors involved, thus reducing it at least to 140/90mmHg and even to lower values if tolerated, lower than 130/80 in diabetic patients and others with very high risk for CVD cardiovascular disease (stroke, myocardial infarction, renal dysfunction, proteinuria), and to achieve the goal level of BP, the treatment should start before significant damage develops.

The American Heart Association (AHA) and the American College of Cardiology (ACC) in its Expert Consensus Document on Hypertension in the Elderly in 2011, recommended a different approach to patients above 55years, considering their comorbilities, according to this fluxogram:

Figure 4-AHA/ACC recommendations for BP in patients above 55 years



(ACC/AHA, 2011)

Various publications have shown poor compliance to prescribed antihypertensive medicament, being this fact responsible for the lack of BP control(Yiannakopoulou, 2005). In the first year of therapy only 60% of the patients will continue the medication (Caro, Speckman, Raggio, & Jackson, 1999)(Massaglia, et al., 2005), and after 5-10 years as much as 60% will abandon their prescription for hypertension(Caro, Speckman, Raggio, & Jackson, 1999). In the ALLHAT trial, prospectively, about 34% of the patients remained with unsatisfactory blood pressure control in spite of in average 2 medications and overall nearly half of the patients would have required 3 or more drugs, and at the end only2/3 of the participants had their SBP lowered to 140mmhg although 92% has the DBP of 90mmHg.(ALLHAT officers and col, 2002). As hypertension is

a chronic disease, the treatment is required for a lifetime. The more increases the number pills and the complexity of dosage the poorer is the adherence to the treatment. Also when more drugs are combined it increases the possibility of side effects. Moreover change the life style is another difficult goal to reach. Frequent visit to the clinic augments adhesion to the treatment.(Stason, et al., 1994)

The use of acupuncture could help overcome these difficulties, by either diminishing or substituting the amount of drug required, and also because with frequent visits to the clinic it eases the compliance to the treatment (drugs and/or adjustment of lifestyle).

2.The Heidelberg Model of TCM or TCM as novel vegetative medicine

Traditional Chinese Medicine is a "system of sensations and findings designed to establish a functional vegetative state of the body and this state can be treated by Chinese pharmacotherapy, acupuncture, Chinese manual therapy (Tuina), Qi gong (biofeedback) or dietetics"(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

In 1989, Kroenke and Mangelsdorf observed that almost 85% of the complaints in the outpatient clinic failed to demonstrate an organic cause, thus it could not be correlated to a measurable laboratory test.(Kroenke & Mangelsdorff, 1989)

Usually these inexplicable complaints could be pointed to psychosomatic disorders. Around 60-80% of the patients that have chronic complaints search for help of complementary medicine.(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed).

The bases for the integration of the Chinese medicine into western world are:

-Rational concept of TCM (rationally accessible)

-Scientific proof of efficacy and safety

-Quality control to be put on the basis of developing knowledge in this medical system

(Greten H. , 2006)

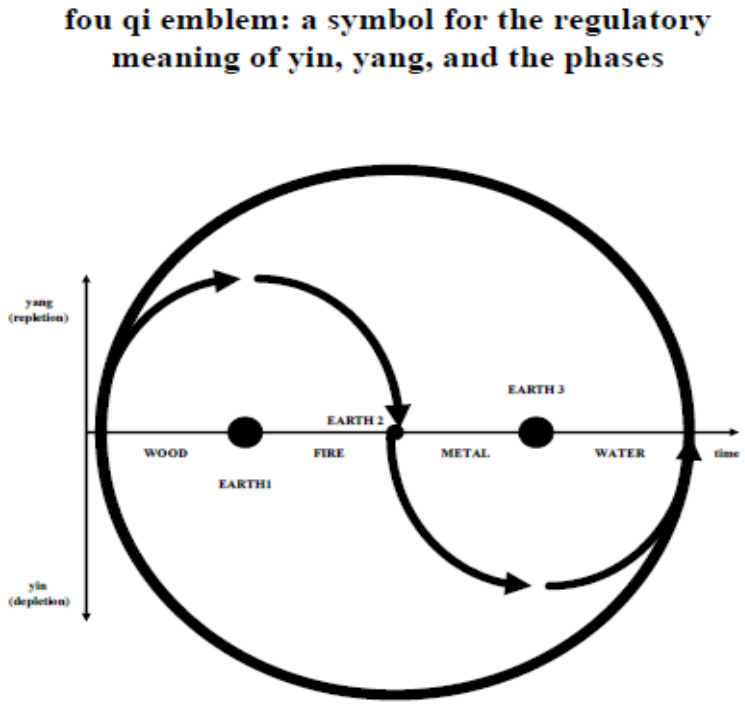
Aiming to allow a rational approach to Chinese medicine. Prof Greten developed the Heidelberg Model of TCM as a scientific model, based on prof. Porkert previous works (Porkert, 1983)(Porkert M. , 1974)(Porkert M. a., 1995) relying on primary Chinese sources. The precise Latin terminology utilized in this HD Model therefore is derived from these previous works.

Leibniz's analysis of the oldest book of the mankind -I Ging ("the Book of Changes") explained the logical model of system biology using mathematical language - binary numbers. Based on this analysis prof. Greten developed a new view of Chinese Medicine. Thus yin is a black (discontinuous) bar and yang is white (continuous) bar and they form monogram, bigram, trigram, and they can be used to describe also circular processes.(Greten H. , 2006)

There is evidence that in Classical China, even before the Yellow Emperor's Classic, these regulatory fluctuations were described by circulatory functions in a

simplistic manner resembling a *sinus wave.* This wave is part of the so- called monad (Leibniz) or Taiji sign

Figure 4- Taiji Sign

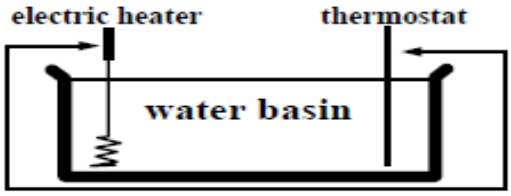


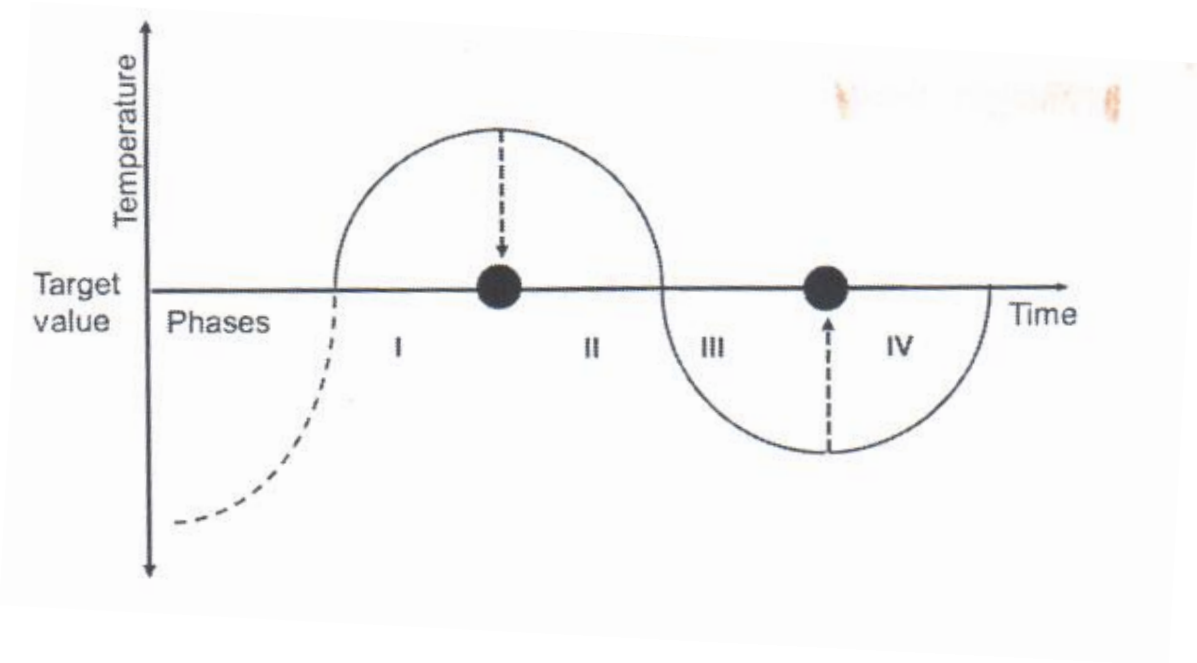
(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

Most of the regulatory processes describe periodical fluctuations of the actual value around a target value. Accordingly, as a vegetative system also is a regulatory process, one could categorize the symptoms leading to the orb- "group of diagnostically relevant signs that indicates the functional state of a body island (body region), which correlates with the functional properties of the conduit"(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed).

To exemplify this situation we could use a model of water basin with an electric heater, which is regulated by a thermostat. A target value in this case could be 37ºC.

Figure 5- Regulation as a sinusoidal curve





(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

In the morning the incubator will be at room temperature. When we switch on the system, the electric heater will switch on because the actual temperature is below the target value and it will take a while until the temperature rises to 37ºC.

Phase I: target temperature is reached and therefore the thermostat turns off the electricity to the heater. Nevertheless the temperature will still rise a little because the heater is still hot (afterheat) In biological scenario: phase Wood

Phase II: this excess afterheat is gradually used up, so the water cools down back to the target value. After cooling down the target temperature, the heater will be turned on again. Phase Fire.

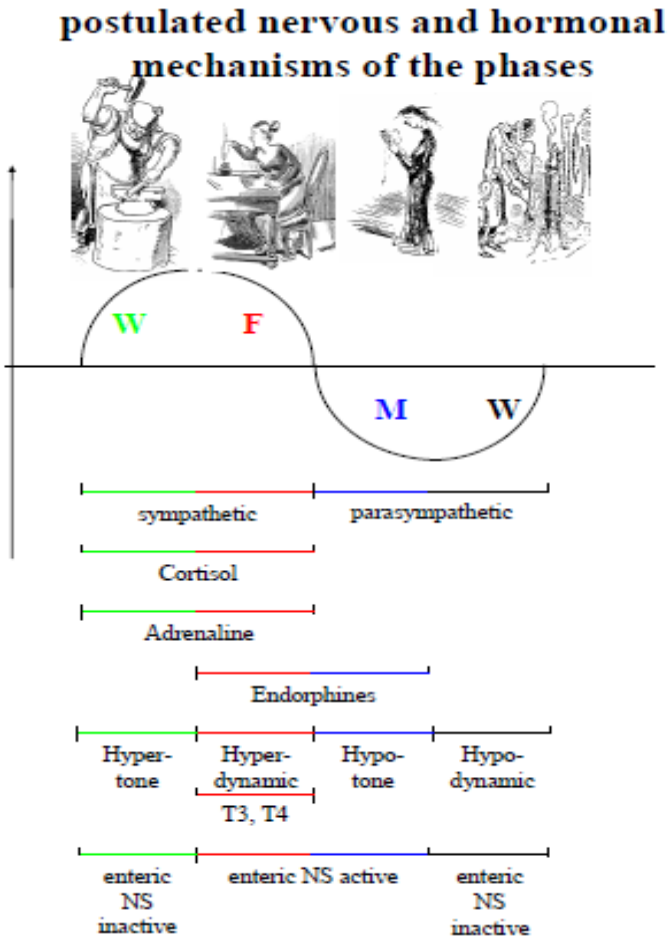
Phase III: The heater is turned on, but it takes sometime until the heater is hot again (latency). Biological scenario; phase Metal

Phase IV: After a while the heater will be warmer than the water, so the temperature and the energy content in the basin will be regenerate (regeneration). Biological system: phase Water

And this will go on and on in a repetitive pattern. This sinus wave, from another perspective, is a circular movement, and the axis of this movement is the target value, the Earth (black dots on the graphic).

And this regulation is not only with temperature, it can be extrapolated to other body systems for example overall vegetative activity of man. High activity will be then yang or repletion; low activity will be yin or depletion. (Here interpretation of yin is below target value and yang above target value).

Figure 6- Phases in TCM and western physiology



(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

The above figure symbolizes in its upper part the clinical appearance of the visible signs of the phases- the coppersmith in Wood with active extensor muscles, higher blood pressure than the lady in phase metal.

(Group of signs-patterns in Chinese medicine). Below the graphic there is a schematic reduced form of the concept of transmitters and neuronal pathways- the western physiological description of a vegetative sinus wave.

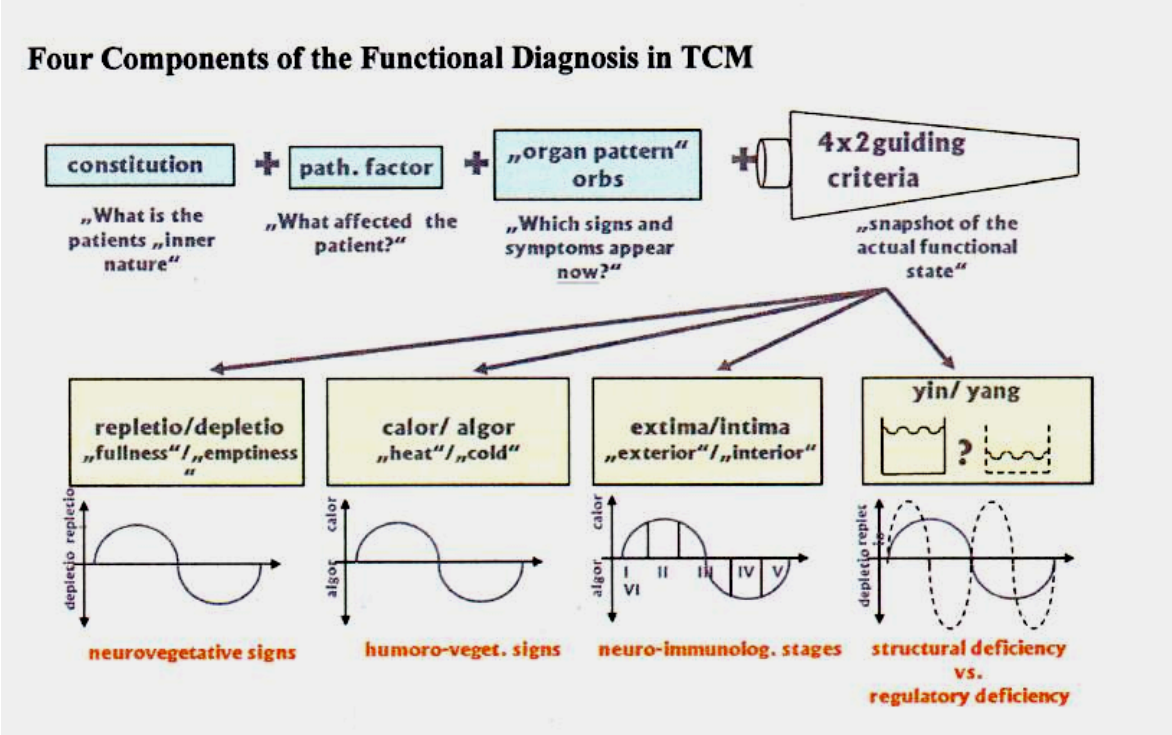
As a scientific proofing this theory, there are a number of studies based on this HD model: for pain following tonsillectomy (Sertel, et al., 2009); polineuropathy (Schroeder, Liepert, Remppis, & Greten, 2007); congestive heart failure (Greten, et al., 2008); walking distance in peripheral occlusive disease (Forschungsemeinschaft, 2006), gait improvement(Hauer K, 2011), qi gong effects(Sousa, et al., 2012)(Matos, Goncalves, Silva, Mendes, Machado, & Greten, 2012)

2.1Diagnosis in Heidelberg Model of TCM:

There are four mechanisms to become sick, according to TCM:

1- Excess of an agent (see below)
2- Problems in transition from one phase to the next
3- Imbalance of antagonist phases
4- Yin deficiency (less substance- so as in water basin example- less water in the basin thus causing higher variations in the temperature

Figure 7-Four Components of Functional Diagnosis in TCM



(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

The figure above shows us a schematic of the TCM diagnosis.

First: **Constitution**- Refers to the inner nature, individual functional properties- based on the characteristics shown externally (physical pattern, way of walking, characteristics of the voice, among others)

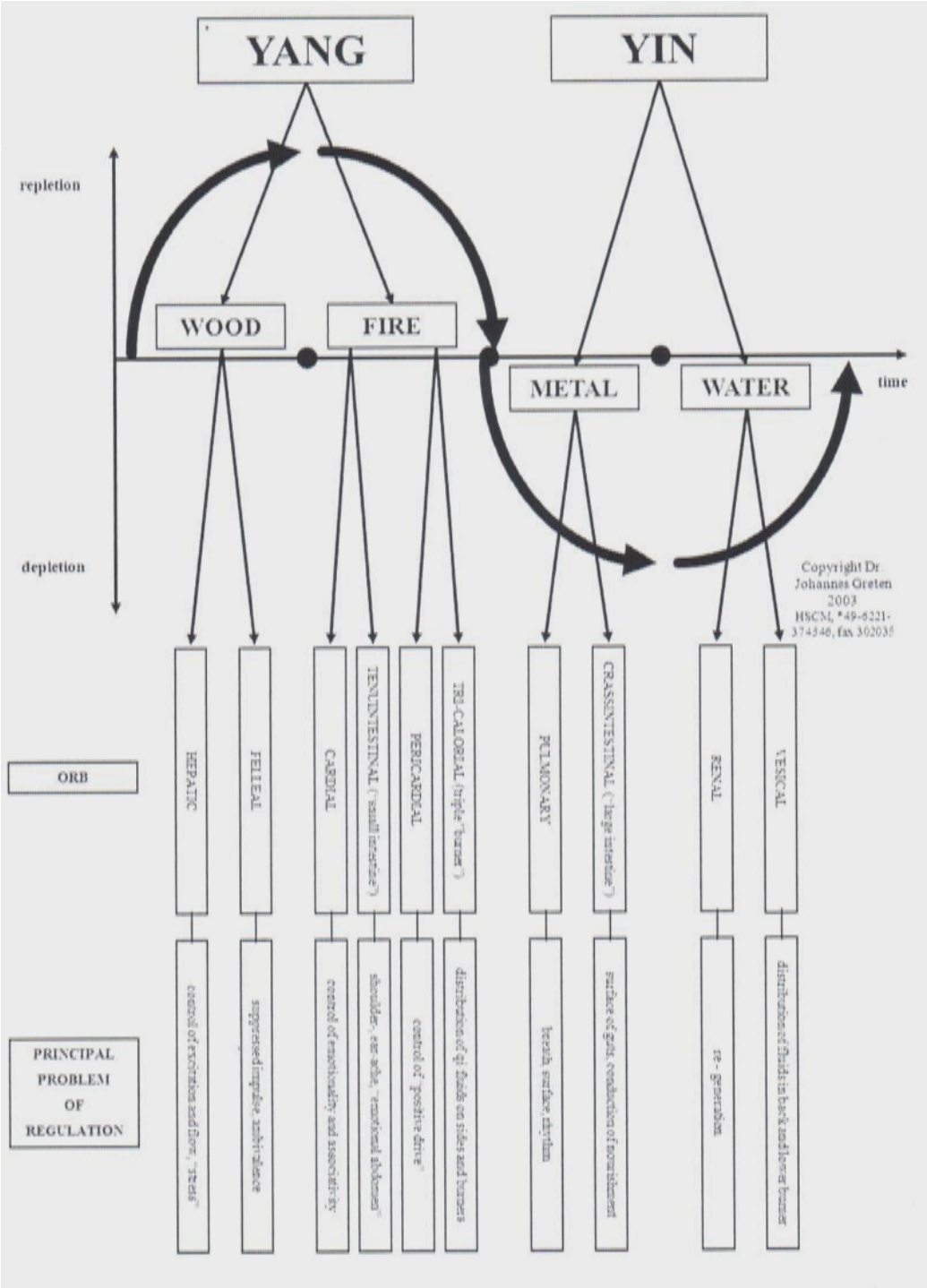
Second: **Agent**- **pathogenic** factor eliciting specific signs and symptoms by changing the individual functional properties (constitution) and/or producing symptoms by itself causing orbs patterns.

Table 4- Agents in TCM

External Agents	Ventus ('wind'), algor ('cold'), humour ('humidity'), ariditas ('dryness'), aestus ('summer heat'), ardour ('glow")
Internal Agents	Ira ('anger'), voluptas ('lust'), cogitatio ('excessive thinking') maeror ('grief'), solicitudo ('worriedness'), timor ('anxiety'), pavor ('shock')
Neutral Agents	overwork, malnutrition, trauma, infections.

Third: **Orb**: "" Group of diagnostically relevant signs and indicate the functional state of the body island, which correlates with the functional state of the conduit; also a clinical manifestation of a phase named after a region of the body"(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

Figure 8- Phases/Orbs and the principal problem of regulation



(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

Forth part of diagnosis in TCM is **Guiding Criteria (GC)**. There are four GC:

1st GC- repletion**/depletion** ('excess/emptiness') originates from qi, orbs, phases in TCM and corresponds to neuro-vegetative signs in western medicine. Repletion indicates too much qi or blockage of the flow causing excess in the pre-blocked area, in general the symptom is worse with pressure, excitation of activating mechanisms as opposed to depletion which indicates lack of qi, amelioration of the symptoms by pressure and indicates lack of activation and/or excess of deactivation)

2nd GC- calor/algor ('heat/cold') in TCM evaluates effects of xue ('blood' functional capacity bonded to body fluids with functions such as warming, moisturizing, creating qi and nourishing a tissue.) and in western medicine refers to signs originated from the humoro-vegetative system, referring to the effects of microcirculation, therefore increased xue activation-increase in microcirculation is called calor, and lack/diminished microcirculation-xue represents algor.

3rd GC- extima/intima (exterior/interior) evaluates the signs caused by an external agent- the most common model is Shan han Lun- Algor laedens theory- ALT- model of six stages algor- (Figure 14) describing the pathogenic process caused by the agent algor, induced by the neuroimmunological mechanisms. Describes the regional lack of microcirculation caused by agent algor as in reflexes in common cold such as complement system, prostaglandins (**stage I-yang major**) counter reaction with general increase in the microcirculation, inflammatory processes, fever-"reactive calor") (**stage II-splendour yang**), as the disease progresses development of fever/cold, nausea occurs (**stage III – yang minor**). Until now the agent is in the exterior-conduits **extima**. When the immune systems is weak the agent penetrates the interior-**intima** causing cough with expectoration, (**stage IV- yin major**) and could worsen to pneumonia (**stage V-yin flectens**) generalized weakness and even death, or gradual recovery (**stage VI-yin minor**)

4th GC- yin/yang evaluates the signs according to TCM to distinguish between primary deregulation (yang) and secondary deregulation due to structural deficiency (yin). If a functional tissue is deficient, there will be excess over regulation to achieve appropriate function, thus leading to exertion of tissue function and function deficiency. In western medicine-a deficient tissue can be vegetatively over stimulated causing signs of repletion-after the exertion signs of depletion will occur-so in this case **yin** represent deficiency of functional tissue,

structural, and/or deficiency of xue (microcirculation), deficiency of body fluids, lack/deficit of jing (cell nucleus- gene). And **yang** – symptoms are more related to the functional aspect, not with the structure.

3.Acupuncture

Acupuncture's history is known to go back to China about 2500-3000 years ago, when there is mention of the first treatment using needles to stimulate certain points. But surprisingly, the "Tyrolean Iceman" who lived about 5200 years ago, has tattoo marks that according to some experts, correspond to acupuncture points leading the suggestion that there was therapy similar to acupuncture in Europe by this time (Dorfer, et al., 1999), suggesting that acupuncture was also applied in western countries long ago.

Figure 9- Example of tattoos on the Tyrolean Iceman

Top, three groups of parallel lines running in longitudinal direction on the left side and one group on the right side of the back (arrows). The groups on the lower left back and on the right side of the spine are barely visible. Bottom, one of the two tattoo crosses found, located above and behind the left, lateral malleolus (arrow). The course of the urinary-bladder acupuncture meridian and the location of urinary bladder

From: The Lancet, vol 354 issue(Dorfer, et al., 1999)with permission

In the beginning needles made of stone were used and nowadays metal needles are employed. More recently acupuncture has been incorporated into the Traditional Chinese Medicine (TCM).

The first official description of Chinese Medicine was in the *Yellow Emperor's Classic on Internal Medicine ("Huangdi Neijing")* dated 2300 years ago,

although it is believed that most of the history of Chinese Medicine dates back around 4 to 8 thousand years-lying in the obscure of history.(Greten H. , 2006). Nowadays we have a group of related acupuncture techniques and styles such as Japanese, Korean, French, Vietnamese and those based on microsystems such as auriculoacupuncture, Korean hand acupuncture and cranioacupuncture.

Acupuncture techniques comprise different procedures such as pressure on acupuncture points (acupressure), use of needle insertion, applying heat usually with Artemisia (moxibustion) (Porkert M. a., 1995), combined with electric stimulus on the needle (electro acupuncture) (Bastos, 1993), use of laser(Litscher G. a., 2012).

It was in the 13th century after the first medical description of the acupuncture by a western physician-William of Rubruck (Bivens, 2000) that the interest in acupuncture appeared and many publications emerged. But the interest in this field fluctuated until 1971, when a US journalist James Reston published in the New York Times that he had received a successful acupuncture treatment after an appendectomy while he was in China- (Reston, 1971). Since this publication in the media, the general interest from lay people has been increasing and many others papers surged. So, in 1997 a ' consensus conference' by National Institute of Health supported that acupuncture could be useful in an array of conditions such as post-operative and chemo nausea and vomiting, dental pain, fibromyalgia among others.(National Institute of Health, 1997). Additionally in 2003, the World Health Organization review stated that acupuncture has been proved for at least 28 medical conditions.(WHO, 2003)

In eastern medicine it is the functional state that is considered, whereas in western medicine it is based on the matter, substratum and expresses their data based on the metric system(Porkert, 1983), therefore it is important to understand the following points in order to comprehend the concepts behind acupuncture: qi, yin/yang, and Five Elements.
Qi (pronounced "chee") is an Immaterial energy with a qualification and direction (Porkert M. , 1974) and "vegetative capacity to function of a tissue or organ which may cause the sensation of pressure, tearing or flow, according to the Heidelberg (HD) Model of TCM –described above). Diseases are believed to be associated with an imbalance deficiency, blockages, causing excess of qi.
Yin and yang are terms used to describe all things in nature and are complementary opposites. Yin is used to represent more material, dense states of matter while yang is functional, represents more immaterial, rarefied states of

matter. And the interaction between the two opposites is dynamic and cyclical. To the acupuncturist, health is a constant state of dynamic balance and one must employ a series of qualitative assessments to establish a patient's present disposition(Maciocia, 1989).

According again to Maciocia, 1989, the Five Elements are wood, water, fire, earth, and metal, interacting to each other. They represent not only the basic constituents of nature, but also represent different basic processes, qualities, or phases of a cycle. Most vital organs, acupuncture meridians or conduits, emotions, and other health-related variable are assigned an element, thus providing a global description of the balancing dynamics seen in each person.

The Chinese Medicine practitioner uses these principles for diagnosis and treatment selection. After determining the imbalance, the objective is to shift the constitution towards balance with the use of some resources. Acupuncture is one important among them. Eastern medicine values the clinician's initial assessment and encourages the practitioner to value his/her own intuition to extract additional information. Eastern thought perceives the world as dynamic and interconnected (Capra, 2000 4th ed)]. Thus it makes little sense to the acupuncturist to isolate a symptom such as back pain. Symptoms necessarily arise from a particular context. Acupuncture treatments are therefore usually individualized, and two patients with the same symptoms often do not get the same treatment, furthermore as this is a dynamic process even the same patient may also not receive the same treatment on every following visit.

The technique of needle insertion depends on the therapeutic effects desired, and on the quality of stimulation intended (dispulsion in repletion or suppletion in depletion), topology of the site, direction of the conduit.(Porkert M. a., 1995)

3.1 Electro acupuncture

Electro acupuncture (EA) is a technique that stimulates the needles with a small electrical current at low frequency (2 to 4 Hz) or high frequencies (100-200Hz) and it seems to be one strong form of acupuncture.(Ulett, 2002) and can induce long clinical response in rats during 1 to 12h(Yao & Anderson, 1982).

In experimental protocols, EA could be preferred to manual acupuncture , when possible, because with EA it is possible to keep a steady stimulation of a period of time that could be measured and is reproducible.(Ulett, 2002)

Comparison of Manual acupuncture (MA) and EA using low-frequency stimulation (~2 Hz) applied for 120 seconds every 10 minutes over a 30-minute period found similar effects on the increase in blood pressure cardiovascular reflex response to gastric distension (pressor stimulus) in anesthetized rats. The only difference in response was a slightly more prolonged effect of EA (effect duration of 30min) as compared to MA (2min every 10min) effect that lasted 20 min after termination of stimulation. Both forms of stimulation caused nearly identical responses of afferent single units recorded in the median nerve.(Zhou, Fu, & Tjen-Looi, Afferent mechanisms underlying stimulation modality -related modulation of acupuncture-related cardiovascular responses, 2005) Also Zhou et al in 2005 observed that sympathoexcitatory sympathetic premotor neurons in the rostral ventral lateral medulla (rVLM) were found to respond similarly to MA and EA, specifically the low current (2mA) and low frequency (2Hz) and not high-frequency EA (40-100Hz). This study raised considerable question about the ability of high-frequency EA to provide afferent input to the CNS to regulate sympathetic outflow (Zhou, Tjen-A-Looi, & Longhurst, 2005)

Another studies with both low and high frequency electro acupuncture can modulate sympathetic motor changes in pain (Ernst & Lee, 1985).

EA at different frequencies causes diverse cardiovascular responses, thus low-frequency (2Hz) causes depressor response (Lee H. a., 1994) whereas High frequent EA can cause pressor response in normal individual(Ernst & Lee, 1985).

3.2.Acupuncture and Cardiovascular System

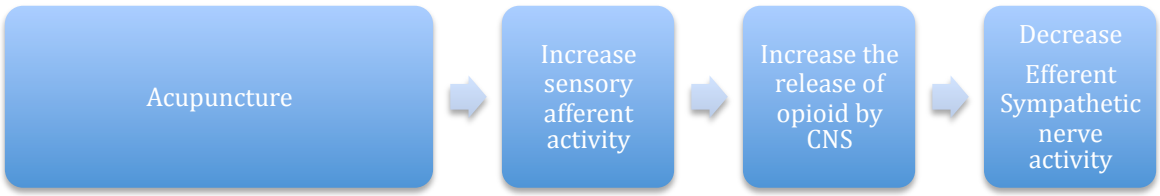
According to the consensus on Complementary and Investigative Medicine published by the American College of Cardiology in its task force(Vogel, 2005), acupuncture could be indicated in four areas in cardiovascular diseases (CVD): Ischemic CVD, hypertension, heart failure (HF), arrhythmias.

The World Health Organization (WHO, 2003)reviewing acupuncture in more than 40 medical conditions, found that acupuncture is effective in hypertension and some coronary heart disease.

The sympathetic activation in the cardio vascular system leads to an increase in heart rate (HR), BP, myocardial contractility an/or myocardial oxygen demand during a pressor stimulus. Therefore the use of acupuncture for these areas of CVD is justified by its ability to inhibit the sympathetic outflow(Yao &

Anderson, 1982), and therefore the cardiovascular sympathoexcitatory effect reflex(Zhou & Longhurst, Neuroendocrine mechanisms of Acupuncture in the Treatment of Hypertension, 2012)(Zhou, Fu, & Tjen-Looi, Afferent mechanisms underlying stimulation modality -related modulation of acupuncture-related cardiovascular responses, 2005) And it could be probably due to the following pathway (Middlekauf, et al., 2002):

Figure 10- Probable pathway for acupuncture action in CVD



The cardiovascular system is integrated, therefore action in BP could also have effects in CHD, treatment for arrhythmias also could have results to decrease oxygen demand and relieve discomfort from CHD, peripheral resistance works not only to reduce the BP but also to decrease the cardiac workload therefore also reduce myocardial ischemia.

3.2.1 Acupuncture and coronary heart disease

Some experimental studies in cats demonstrated reduction in myocardial ischemia by reducing oxygen demand instead of increase in coronary flow(Li, Pitsillides, Rendig, Pan, & Longhurst, 1998). Another study in chinchilla rabbit showed improvement in acute myocardial ischemia after electro acupuncture.(Cai, et al., 2010). Also there seems to be a cardio protection of reperfusion injury by modulation of norepinephrine release, apparently via

inhibition of cardiac nervous system in an opioid and protein kinase C dependent pathway.(Zhou, et al., 2012)

Richter and colleagues, in a placebo controlled, cross over study design (Richter, Herlitz, & Hjalmarson, 1991) showed that manual acupuncture reduced in episodes of chest pain and its magnitude and improvement in ST depression and increase in work load to elicit chest pain as assessed by exercise test. Also improvement in exercise test was observed in other studies(Ballegaard, Jensen, Pedersen, & Nissen, 1986)(Ballegaard, Pedersen, Pietersen, Nissen, & Olsen, 1990).

In a study using acupuncture in Pc6 (neiguan), Kurono et al(Kurono, Egawa, Yano, & Shimono, 2002) showed a vasodilatation in coronary arteries in some patients with coronary stenosis, but no vasospastic or syndrome X, without inducing systemic hypotension.

Those studies were either experimental or with a small group of patients and larger well-designed studies are granted in this subject.

3.2.2 Acupuncture and Heart Failure

A clinical pilot study by Middlekauff et al. *(*(Middlekauf, et al., 2002) with fifteen advanced heart failure patients that underwent acute mental stress testing before and during a single session of real acupuncture demonstrated surges in sympathetic activation during mental stress (a potent stimulus to the autonomic nervous system) were eliminated by acupuncture. As the patients were submitted to only one session of acupuncture, these findings cannot be extrapolated to the normal average 10 sessions acupuncture performed in clinical practice. The authors concluded that acute acupuncture attenuates adrenergic excitation during mental stress in advanced heart failure patients.

Kristen et al(Kristen, et al., 2010) in a pilot study observed that an increase in exercise tolerance by patients with heart failure as assessed by ambulated 6-minute walk distance after acupuncture.

Heart rate variability is a prognostic indicator in heart failure(Ponikowski, 1997) and some studies has been carried showing the effects of acupuncture on it(Huang, Chen, Lo, Lin, Lee, & Kuo, 2005; Bobkova, Gaponiuk, Korovkina, Sherkovina, & Leonova, 1991; Bobkova, Gaponiuk, Korovkina, Sherkovina, & Leonova, 1991) (Litscher G. , 2007)(Hsu, Liu, Tsai, & Chang, 2006)(Kristen, et al., 2010).

3.2.3 Acupuncture in arrhythmias

Acupuncture can inhibit ventricular premature beating (extra systoles) by stimulating the hypothalamus, paraventricular nucleus(Guo, Jai, Cao, Guo, & Li, 1981) or after administration of BaCl2(Li & Yao, Mechanism of the Modulatoty Effect of Acupuncture on Abnormal Cardiovascular Functions, 1992).

Here again the rationale for its application sits on the ability to inhibit the sympathetic outflow.(Yao & Anderson, 1982).

In anesthetized rabbits the number of ventricular extra systoles induced by stimulus in hypothalamus was reduced by electro acupuncture in S36 and Pc6 acupoints, whereas stimulation of superficial peroneal and superficial radial nerves elicited excitatory responses. Further experiments showed that this inhibitory action of S36 and Pc6 was due to inhibition of the cardiac sympathetic centre in rVLM, and acts through opioid, GABA and 5-HT receptors in this region. Conversely the excitatory response may be related to activation of cholinergic response in the same rVLM(Li & Yao, Mechanism of the Modulatoty Effect of Acupuncture on Abnormal Cardiovascular Functions, 1992)(Guo X. L., 1986).

As for bradicardia, EA applied to superficial peroneal nerve or superficial radial nerve produced partial blockage of the bradicardia provoked by stimulus in the aortic nerve or nucleus tractus solitary. Also stimulus with high current in deep peroneal or median nerve blocked this bradicardia. It was demonstrated that activation of cholinergic receptors in rVLM contributes to suppress vagal evoked bradicardia. This activation in rVLM inhibits both baroceptor sensitive neurons in the dorsal vagal nucleus and nucleus ambigus. GABAergic and opioids may play important role in mediation of this reflex inhibition.(Li & Yao, Mechanism of the Modulatoty Effect of Acupuncture on Abnormal Cardiovascular Functions, 1992)(Wang, Guo, & Li, The inhibitory effect of somatic imputs on the excitatory resposes of vagal cardiomotor neurones to stimulation of the nucleus tractus solitarius in rabbits, 1988)(Wang & Li, A GABAergic mechanism in the inhibition of cardiac vagal reflexes, 1988)

3.2.4 Acupuncture and Hypertension

Acupuncture can have an antihypertensive through a milieu of ways, levels and factors, balancing and integrating the cardiovascular system, nervous system, endocrine and hormone regulation.(Zhang R. H., 2007)

There are publications in China as early as in the 50's, pointing the success in lowering the BP(Zhang C. , 1956), since then, there have been many studies of the effects of acupuncture in the hypertension.

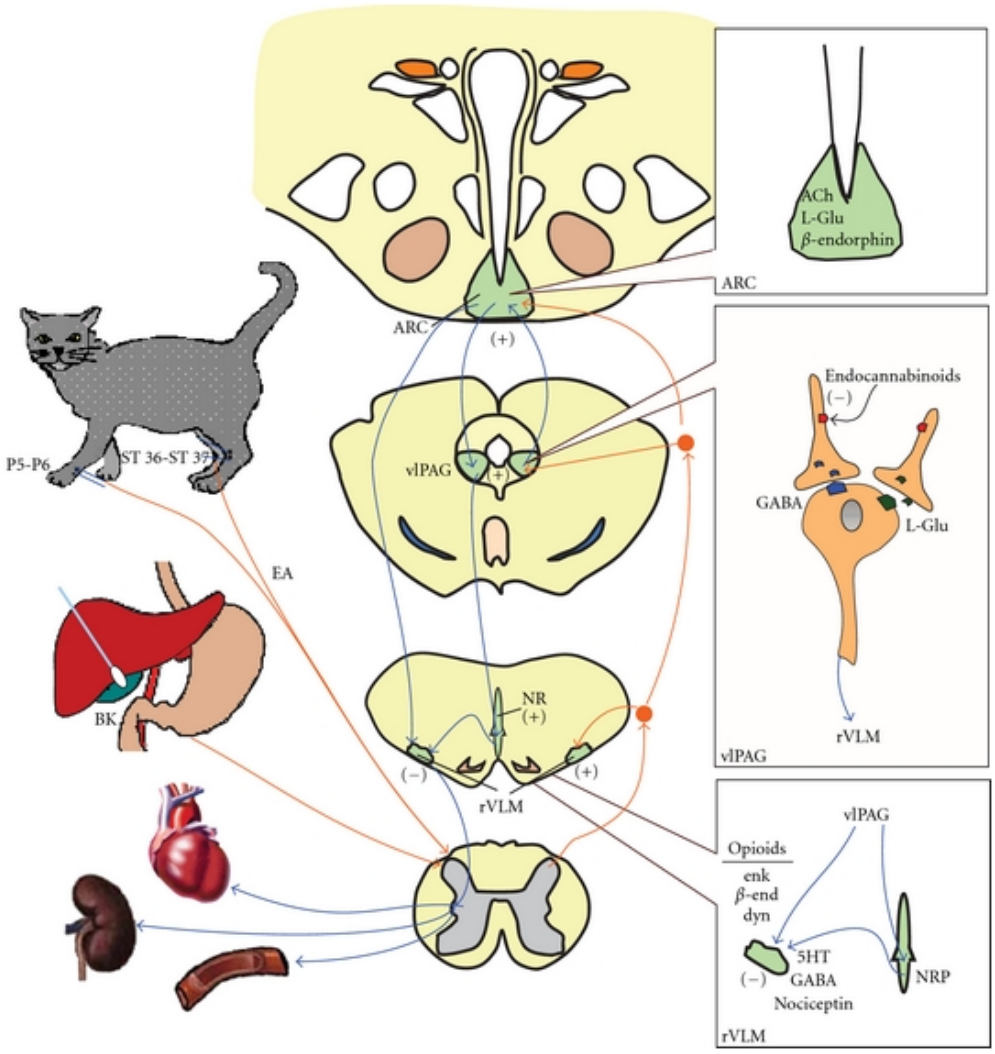
The central nervous system plays an important role in the development and maintenance of hypertension. Increased sympathetic activity and alteration in arterial baroreflex function may contribute to the development of hypertension. (Veerasingham & Raizada, 2003)

An augmented sympathetic tone leads to an arteriolar vasoconstriction and by increasing the force and rate of contraction of the heart to increase cardiac output. As BP=CO X RP, here, there is an important direct action of increased sympathetic activity on hypertension. Also increased renal sympathetic activity leads to an increase in production of Renin. Renin activates the conversion of angiotensinogen into angiotensin I. The ACE converts angiotensin I in angiotensin II, which can cause vasoconstriction (rise in peripheral resistance) per si, and also stimulate aldosterone, causing salt retention, both mechanism that contributes to the elevation of the blood pressure.(Zhou & Longhurst, Neuroendocrine mechanisms of Acupuncture in the Treatment of Hypertension, 2012)

Carotid sinus and aortic arch baroceptors acts modulating parasympathetic and sympathetic outflow in response to changes in BP. Nevertheless an elevated blood pressure with time leads to a resetting of the baroceptors to a higher pressure, contributing to the perpetuation of hypertension.

In hypertensive animal model there are changes in CNS, mainly in hypothalamic and medullar areas that modulate sympathetic flow.(Colombari, Sato, Bergamaschi, Campos, & Lopes, 2001). Angiotensin II apart from its direct action in vasoconstriction, indirect action via aldosterone also acts at various hypothalamic and medullar areas to enhance sympathetic outflow, alters the sensitivity of baroceptors and stimulates secretion of vasopressin.(Averill & Diz, 2000)(Dampney, Fontes, Hirooka, Horiuchi, Potts, & Tagawa, 2002)

Figure 11 Neural circuits of acupuncture's action in reflex blood pressure modulation



Neural circuits of acupuncture's action on cardiovascular sympathoexcitatory visceral reflex elevation of blood pressure. Abbreviations: ARC: arcuate nucleus; vlPAG: ventrolateral periaqueductal gray; NR: nuclei raphe; rVLM: rostral ventrolateral medulla.

From:Evid Based Complement Alternat Med. 2012; 2012: 878673.

EA in the rVLM

The rVLM plays a critical role in the control of BP and inhibition of the functions in this nucleus decreases significantly the BP.(Guertzenstein, 1974)In fact, EA inhibited the elevation of BP and sympathetic neural activity in the rVLM following gastric distension (pressor stimulus) in rats. (Zhou, Tjen-A-Looi, & Longhurst, 2005).

This nucleus and its premotor sympathetic neuron seem to be very responsive to deep nerves stimuli (median- Pc6 in acupuncture, radial-IC11 as acupoint) (Tjen-A-Looi, Li, & Longhurst, Medullary substrate and differencial cardiovascular responses during stimulation of specific acupoints, 2004). The EA action is inhibited by a non-specific opioid antagonist (naloxone) and also by a GABA blocker suggesting at least part of the action of this intervention is via opioid (ß endorphin, endomorphin and enkephalin but not dynorphin) and GABA(Tjen-A-Looi, Prolonged inhibition of rostral ventral lateral medullary premotor sympathetic neurons by electroacupuncture in cats, 2003) Also nocioceptin and serotonin seem to be involved. (Han J. , 2004).

Different frequencies of EA stimulate different somatic fibers: Low frequency EA (2-4Hz) activates μ ∂ receptors releasing endomorphin, encephalin, ßendorphin and lowering the pressure while high frequency 200Hz stimulate k receptor and releases dynorphin (a potent analgesic).(Han J. S., 2003)(Han J. , 2004) Chao et al(Chao, Shen, Tjen-A-Looi, Pitsillides, Li, & Longhurst, 1999)showed reversal of the sympathetic response to EA after naloxone, but only after those elicited by low frequency (4Hz) and not those induced by high frequency (200Hz). EA seems to act also by reducing the plasma serotonin and norepinephrine. (Zhou, et al., 1995).

The point specificity in lowering the BP has been shown in a study where they used negative and positive electrodes in adjacent points observed that stimulus in Pc5-Pc6, IC10-IC11, IC4 -IC7 and S36-S37 effectively lowered BP whereas IC6-IC7 and S37-S39 did not. (Tjen-A-Looi, Li, & Longhurst, Medullary substrate and differencial cardiovascular responses during stimulation of specific acupoints, 2004).

Important centres in sympathetic tone control:

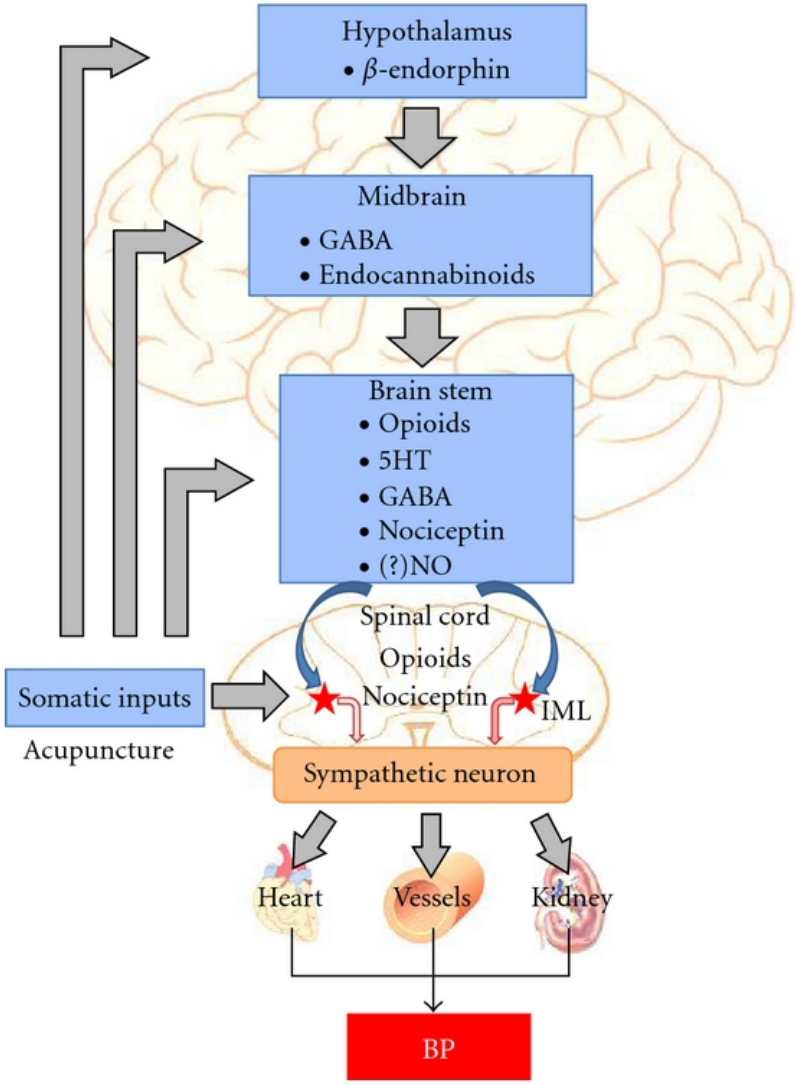
- Hypothalamus arcuate nucleus (central) and is an important source of opiates that are transported to regions such as rVLM(Guo & Longhurst, 2007), and also stimulates the vlPAG(Li, Tjen-A-Looi, & Longhurst, Excitatory projections from arcuate nucleus to ventrolateral periarqueductal gray in electroacupuncture inhibition of cardiovascular reflexes, 2006)
- vlPAG (midbrain) is a cardio depressor region- send directly or indirectly inhibitory inputs to rVLM reducing sympathetic flow and thus inhibiting the elevation in BP to a pressor stimulus(Tjen-A-Looi,

Li, & Longhurst, Midbrain vlPAG inhibitis rVLM cardiovascular sympatoexcitatory responses during electroacupuncture, 2006)

- NRP-medullar nucleus raphé pallidus –receives projections from vlPAG and may act through serotonin receptors in the rVLM acting in modulation of cardiovascular activity
- rVLM (see above)

EA can act directly or indirectly in these centres thus modulating the cardiovascular responses.(Zhou & Longhurst, Neuroendocrine mechanisms of Acupuncture in the Treatment of Hypertension, 2012)

Figure 12 Neuroendocrine modulation of Blood Pressure by acupuncture



GABA γ-aminobutiric acid; 5HT-5-hydroxytryptamine or serotonin; NO:nitric oxide, IML:intermediolateral column of the spinal cord

From: Evid Based Complement Alternat Med. 2012; 2012: 878673.

In stress-induced hypertension in rats, stimulation of the deep peroneal nerve (DPN) underneath the Zusanli (S36) acupoint with a low current and low frequency for 10 min reduced BP markedly with a nadir occurring 1 h later. Microinjection of naloxone into the rostral ventrolateral medulla (rVLM) blocked this depressor effect, suggesting that this depressor effect is related to the activation of opiate receptors in this region of the medulla.(Xie, 1997)

In anesthetized open-chest dogs, EA in acupoint Neiguan (PC6) provided a stable cardiovascular function under normotension and an anti-shock effect on haemorrhage-induced hypotension, whereas in conscious dogs EA applied to *Zusanli* (S36) with a current of 2-4 V, 1-100 Hz had no significant effect in normotensive dogs. However, after continuous endovenous noradrenalin administration at a constant rate and raising of systolic blood pressure to 178/20 mm Hg (a level that could be kept for more than 1 h) EA was then applied to Zusanli or Neiguan acupoints for 20-30 min and a decrease of blood pressure (BP) by 20-30 mm Hg, a statistically significant effect compared to the basal BP before EA or control group ($P < 0.01$). BP was maintained at low level during EA and returned slowly to the pre-EA high-level 30-40 min after EA was terminated. This inhibitory effect of EA was not found in anesthetized dogs. Further analysis showed that the depressor effect of EA is mainly caused by vasodilatation of mesenteric vessels and due to inhibition of sympathetic vasoconstrictor tone. Experiments also showed that the depressor effect of EA in this kind of hypertension was due to the inhibition of arterial chemoreceptor pressor reflexes, but not to the activation of the baroreceptor reflexes. The central inhibition of EA was related to the activation of opiate receptors in the periaqueduct gray (PAG), hypothalamic supramammillary area and the dorsal hippocampus. (Syuu, et al., 2001)

Activation of eNOS (endothelial nitric oxide synthase) and nNOS (neuronal nitric oxide synthase) is one of the mechanisms through which ST- 36 electro acupuncture reduces blood pressure, as observed by Kim et al. with a model two-kidney, one-clip renal hypertension (2K1C) hamster model, submitted to thirty-minute daily electro acupuncture treatment for 5 days leading to a reduction in mean arterial pressure from 160.0 ± 7.6 to 128.0 ± 4.3 mmHg (mean ± SEM), compared to 115.0 ± 7.2 mmHg in sham-operated hamsters, confirming the hypothesis that acupuncture on acupoint stomach 36 point (S36) reduces hypertension by activating nitric oxide synthase signalling mechanisms. (Kim, et al., 2009)

Using awaken adult spontaneous hypertension rats (SHRs) and their normotensive controls, Winstar-Kyoto rats (WKY), after stimulation of the sciatic nerve with low frequency and low current for 30 min to mimic EA, BP was decreased 20 mm Hg below the pre-stimulation level, and did not fully recover to its high pre-stimulation level until 12 h after the termination of sciatic nerve stimulation. The HR and splanchnic sympathetic discharge outflow decreased in parallel with BP. WKY rats revealed no significant response of BP and HR following sciatic nerve stimulation. The long-lasting post-stimulation depressor response was unchanged by sino-aortic nerve transection. They reported the use of a 75 current for the stimulation of the sciatic nerve to elicit a depressor effect that was above the threshold for activating group III fibers. Further study showed that endorphins and serotonin were involved in the post-stimulation depressor response. (Yao & Anderson, 1982)

As increased renal sympathetic activity leads to an increase in production of Renin, thus another mechanism that can explain the effects of acupuncture in hypertension is via decrease in the plasma renin, aldosterone and angiotensin II activity (Anshelevich, Merson, & Afanas'eva, 1985)(Huang H. a., 1992)(Chiu, Chi, & Reid, 1997) and this has a similar action of ACEi. In fact, lower angiotensin I levels were found in hypertensive patients who received acupuncture when compared to a control group of hypertensive patients who did not receive acupuncture (Chiu, Chi, & Reid, 1997). Increased excretion of sodium also was observed following acupuncture.(Yao T. , 1993)

Acupuncture can modulate the neurohumoral system as seen on reduced plasmatic norepinephrine, serotonin and endorphin levels after this procedure.(Middlekauf H. Y., 2001)(Zhou, et al., 1995)

Influence on secretion of the endothelium, regulating the balance between contraction factors (EDCF-endothelium derived contraction factors) and relaxation (EDRF Endothelium Derived Relaxation Factor) also seems to play a role in the usage of acupuncture to treat hypertension (Zhang R. H., 2007)

A review of literature reveals various reports showing the effectiveness of acupuncture on blood pressure and other hemodynamic parameters in humans(Flachskampf, et al., 2007) (Yin Z. , 1998)(Anshelevich, Merson, & Afanas'eva, 1985; Kearney, Whelton, Reynolds, Muntner, Whelton, & He, 2005)(Huang H. a., 1992)(Bobkova, Gaponiuk, Korovkina, Sherkovina, & Leonova, 1991)(Dovgiallo, 1987) (Williams, 1991)(Tam, 1975)(Radzievsky, Lebedeva, Fisenko, & Majskaja, 1989)(Monaenkov, 1984)(Akhmedov, 1993)(Dong, 1996) ,

but only a few of them controlled, specially in western community.(Macklin, et al., 2006)(Lee, Kim, Park, Kim, Lee, & Park, 2009)

The SHARP (Stop Hypertension with the Acupuncture Research Program) pilot study, randomized, controlled, although not designed to detect small effect, is a large study on acupuncture for hypertension. The authors concluded that active acupuncture provided no greater benefit than invasive sham acupuncture in reducing systolic or diastolic BP, (Macklin, et al., 2006), but the analysis were done considering just the BP measurement in the office visits, not measuring the 24 ABPM, therefore it haven't measured the BP reducing effects through a larger period in daily life, thus some other factors such as white coat hypertension could be influencing the results. Moreover this method can 'measure more accurately than clinic BP the extent of BP reduction induced by treatment' (ESH/ESC, 2007)

Nevertheless, in a more recent, well designed study, Flachskampft et al. randomized 160 patients, 140 finishing the treatment and found a significant difference in the decrease in 24 hour SBP by 6,4mmHg and 3,7mmHg DBP. (Flachskampf, et al., 2007).

Also in a well-designed double-blinded, randomized, controlled trial a significant long-term antihypertensive effect of acupuncture was reported. It was shown a BP declines of 14.8/6.9 mmHg in their active acupuncture group (n=15) versus 4.0/1.1 mm Hg in the sham group (n=15; p=0.05) after 16 sessions -8 weeks of twice-weekly treatments.(Yin, et al., 2007)

In addition, a recent study (Kim, et al., 2012) a decrease in the nocturnal diastolic dipping was significantly different between active and sham acupuncture group, suggesting that this treatment could be useful to improve the circadian rhythm of BP in patients with hypertension.

4. Hypertension in TCM view

The Chinese Medicine focus on a deeper level of the concrete disease and individually, instead of in the syndrome conception.(Zhang R. H., 2007)

After 35 years of age, there is a great deficiency of structure (yin), which potentiates an excess of the activity of the functions of the body (repletion), due to a greater lability of the vegetative functional capacity (Qi). Therefore the hypertension is a result of the yin/yang (structure/function) imbalance and also an imbalance between hepatic and renal (potential-regeneration)(Zhang R. H., 2007)(Nghi & Recours-Nguyen, 2010)

The main pathologic alteration of hypertension is in the hepatic orb (functional potential dysfunction) .The structure of the potential activity (hepatic yin) is always in deficiency in the hypertension. The vegetative capacity of functional potential and activity for induction of this potential (hepatic qi and hepatic yang) are always in excess(Zhang R. H., 2007)(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

The relation of the hypertension with the hepatic yin and hepatic yang has been studied in many fields such as in endogenous vasoactive substances, plasma polypeptides, immunological factors, sensitivity to sodium, insulin resistance, blood pressure dynamics, blood pressure variability, cardiac remodelling and cardiac function.(Zhang R. H., 2007)

4.1 Acupuncture for the treatment of Hypertension/ TCM view:

The pathomechanism according to TCM are: ventus, calor, humor/pituita, yin deficiency and stasis.(Zhang R. H., 2007)

There are many efficient methods to treat hypertension, such as “cleaning” the hepatic orb and dispels Ventus (as an external agent-phase wood), support the hepatic and renal yin deficiency, eliminate calor and promote diuresis, however the main thing of the therapy, according to many clinical reports is “to calm down the hepatic orb, suppressing the yang” (suppressing the increased sympathetic system)

The points were selected in order to:

-support the yin (corporal substance)

-promote the regeneration of the damaged end organ

-promote sedation and repletion of the hepatic yang (negative feedback of the primary functional problem and excess activity of the hepatic function)

-support the orthopathy – (eu-fuction)

- comproved action in previous studies

4.1.1 The theory of acupoints or how to choose an acupoint:

4.1.1.1 Theory 1: Conduits

Conduits are a line connecting acupoints with a similar effects.

4.1.1.2 Theory 2: The theory of the five inductories (or five antiques)

In old China, conduit was illustrated as being similar to a river running from the nails to the body.

So it explains the flow dynamics of qi -valid for internal, yin orbs (see below).

1. First point-distal point close to the nail bed is **Puteal-**

   This point is equivalent to a main tap, activating the orb in an ON/OFF fashion, used in drastic situation like a collapse, breaking down when it is used in a suppletive manner or in a dispulsive manner in uprising yang such as hypertensive crisis.

   Associated with phase **wood**

2. Second point: pressure relieving valve –**effusory**

   This point is used in acute repletion or acute calor, diminish the excessive potential, so the phase is **fire**

3. Third point: point for fine regulation of the already established flow, FINE TUNNING of the flow. (point of original qi)**-inductory** induce an influx in the orb (suppletive) or an outflow-to relieve the excess in the interior, in order to regulate the interior and exterior qi. Due to these regulating characteristics to eu-function this point is phase **earth.**

4. Fourth point: compared to a pump to transport the qi furthermore along the conduit-**transitory**, normally used when an agent blocks the flow of qi in the conduit. Distribution the qi is function of **metal.**

5. Fifth point- **conjunctory**-is the place where energies goes to the yin. Used to strengthen the yin in many chronic diseases, regenerating-so associated to **water**

Those phases allocations described above are for the internal, horreal or yin orbs because the **qi** is primary **built up** in the **yin** conduits and **stored** in the external (aulic or **yang)** conduits.

4.1.1.3 Theory 3: coupled conduits and coupled effects.

This theory says that the internal and external conduits of a phase are coupled- dispulsion in one side, results in suppletion at the respective point in the other side. The internal e external orbs are:

Table 5- Phase-Internal and External Orbs

Phase	Internal(horreal, yin) orb	External (yang,aulic) orb
Wood	Hepatic	Felleal
Fire	Cardial, Pericardial	Tenuintestinal,Tricaloric
Earth	Lienal	Stomach
Metal	Pulmonar	Crassintesinal
Water	Renal	Vesical

So according to this theory we have (Figure 13)

The **puteal** in the internal orbs is wood; in the external they are **metal,** because metal controls wood.

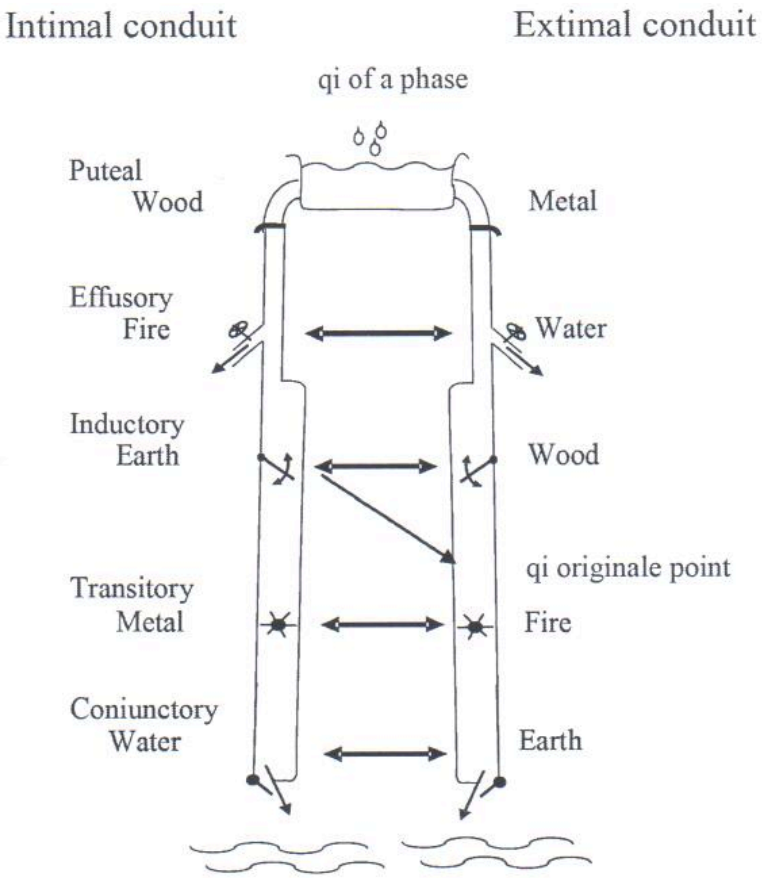
The **effusory** in internal orbs is fire; in the external orbs they are **water**, as counteracting to fire

The **inductory** is earth in the internal orbs, in the external they are **wood** to balance the effect on the other side, and also because it is often used in a suppletive way to enhance energies in the extima.

The **transitory** in the yin orbs is metal, so in the external it is **fire** to express the counter balancing effect on internal transitory

The **conjunctory** is water on the internal orbs, whereas in external it is earth to express the counterbalancing effect on the internal conjunctory.

Figure 13-Coupled conduits and allocated phases



(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

4.1.1.4 Theory 4: Algor Laedens Theory (ALT) or Shan Han Lun (Figure 14)

"The stages of the ALT are featured by specific clinical signs, the understanding of which is an absolute must for the professional practitioner of TCM" (Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

There are six layers of energy constituting six stages of defence:

I layer- defensive qi (wei qi)- it is distributed in the extima, outside the conduits, and it is the first layer of defence against agents. As algor is a lack of microcirculation in western terms, or as a de-activation of xue in eastern terms, it may affect those conduits first, which contain more xue than qi.

The vesical conduit is affected which distributes xue in a segmental fashion over the body.

Xue is controlled and moved by the cardiac orb. The corresponding exterior orb is the tenuintestinal orb and is therefore prone to be affected by algor as an exterior agent.

Thus we have the **Stage I (yang major or taiyang)** and the orbs affected are Vesical and Tenuintestinal. And the main symptoms are: cold shivering, goose bumps, and in the hypertension settings we could have pain in the neck, stiff neck, headache, pressure between the eyes.

II layer- conduit qi- it is the qi inside the conduits (cardinal qi). When an agent blocks the flow of qi, this firstly originates pain and secondary functional disorders in the respective orb.

When the agent algor enters the conduits, this leads to a regional block of flow of qi and xue. Qi flow is blocked more easily than the flow of xue as "qi moves the xue". This is why phases and orbs are more prone to this affection if they depend more on qi. The stomachal and crassintestinal conduits depend more on qi.

"All depletion is a depletion of the Centre" is an old rule of TCM indicating that the Centre is especially prone to a lack of qi. The external conduit of Earth, the stomach conduit, is therefore most easily affected in this stage.

Depletion, as seen in the sinus wave, may lead to signs of the phase Metal, as this phase is depletive in nature and directed downward. This is why the external conduit of this phase, the crass intestinal conduit, is also easily affected in this stage.

So this is **Stage II (splendour yang or yangming).** Here, as agent blocks the conduit qi, the microcirculation is activated in order to expel the agent – **reactive calor**

The main symptoms are: tearing pain as seen in sinusitis, in the hypertension context: swellings of the face, impaired, unclear vision, weakness and pain in thigh and knee, pain in the neck, shoulder and forearm.

III layer- conduit xue- qi in the conduit moves the xue so the warming, moisture and nutrients reach the tissues.

Xue and qi derive from the interior and are led through the system of conduits. If the agent algor overcomes xue flow within the conduit, this may lead to a reverse xue flow into the interior. Also algor reaches the interior, causing the sensation of inner cold.

Often, xue from the inside (the yin) will be mobilised against the agent causing the sensation of internal heat again, or, if the agent algor is driven out, even temporary heat of the exterior, i.e. the skin (extima). Literally, it is said that the agent and xue flow within the conduit play "Tom and Jerry", driving each other in and out repeatedly.

Mobilisation of internal heat is a feature of the phase Wood (mobilisation of potential), and, as this is still an extimal stage, leads to affection the **felleal conduit**.

Also, this causes symptoms and signs of "imbalanced distribution" of energies, which is a principal affection of the **tricaloric orb**.

Thus affection of this defence line leads to **Stage III (yang minor or shaoyang).**

The symptoms usually are: inability to lie on one side of the body, nausea, discomfort ("nagging"). Also: hemicranalgia, loss of hearing, tinnitus, tear pain of the eyes, pain in the neck, on the chest.

IV layer- Body **island qi**- qi within the whole body's interior (intima) where the functions of the orbs are generated in their respective parts of the body ("island"-organs residing more or less in the same region)

All interior affections tend to start with a functional disturbance, so the body islands of the orbs are firstly affected in their function (qi).

When an agent affects qi of the body islands, the lienal and the pulmonary orb are more often affected, as the Centre and Metal are sensitive to diminished activity of qi.

Affection in this layer is called: **Stage IV (yin major or taiyin) .**

The symptoms are: bronchitis, cough, mucus but could also be accumulation of humor and pituita, aggravation of metabolic disorders, swellings of all kinds.

V layer- Body island xue: that is the substance (yin) part of the body island that warms, functionally activates and enhances properties

When algor affects xue within the interior, orb functions depending on xue are more easily affected than others.

As the hepatic orb is considered to be the mare xue ("sea of blood"), hepatic orb functions may be impaired. Also pericardiac signs may appear.

Affection here leads to **Stage V (yin flectens or jueyin)**

Symptoms such as in pneumonia (muscular weakness, undecidedness and demotivation, inability to stand up and also symptoms of the chest, heavy breathing, palpitations, lack of drive.

VI layer- Yin- functional tissue- subpopulation of cells from which the function (yang) develop

The renal orb depends on the yin, and the cardiac orb is the yin side of xue (the yang side of xue is the pericardiac orb).

As yang arises from the yin (in the language of the fourth Guiding Criterion), an analogue process in the technical terms of the first Guiding Criterion is the development of yang qi upwards which is in a rapport with the cardiac qi. This connection is also expressed by the terms of a reno-cardiac axis, the yin pole of which is the renal orb and the yang pole is the cardiac orb.

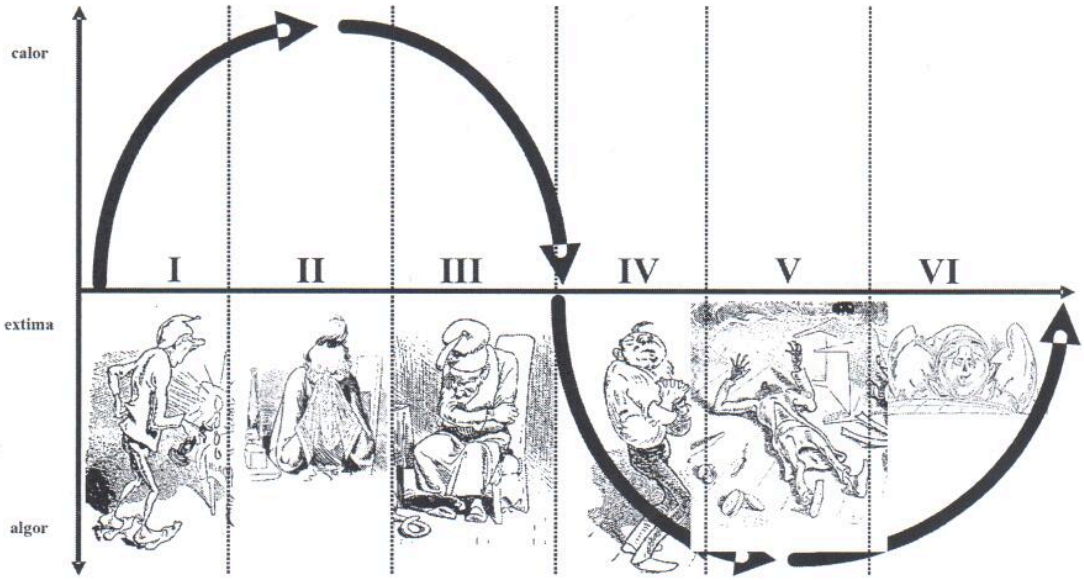
When the yin is affected we have: **Stage VI (yin minor or shaoyin).**

The symptoms usually are: lack of power in the knees and in the back, inability to get up, reduction of mind will, tendency to timor (anxiety), problems of memory, prolonged regeneration, reconvalescence and can also have loss of consciousness, fainting, circulatory problems of all kinds, problems also in short-time memory, problems with mental presence, with heart rhythm, pain in the chest, loss of eye sight, hearing and sensory vigilance

The stages, orbs related, clinical signs, stage hopping can be seen in the chart below:

Figure 14- Algor Laedens Theory- Shan han lun

"ALT" algor laedens theory	Stage 1= Yang major taiyang	Stage 2= Splendor yang yangming	Stage 3= Yang minor shaoyang	Stage 4= Yin major Taiyin	Stage 5= Yin flectens Jueyin	Stage 6= Yin minor shaoyin



Symptoms of phases „catchword"	„Sciatic and ear pain"	„Acute sinusitis"	„Hot-cold-nausea-phase"	„Mucus and bronchitis"	„Flat-down-phase" („pneumonia")	convalescence
Involved conduits and orbs	V - IT	IC - S	F - TK	P - L	H - PC	R - C
Linked con-duits and orbs	R - C (2^{nd} circuit)	P - L (1^{st} circuit)	H - PC (3^{rd} circuit)	IC - S (1^{st} circuit)	F - TK (3^{rd} circuit)	V - IT (2^{nd} circuit)
Exemplary decoction	Dec. Ephedrae, Dec. Ram. Cassiae	Dec. Ancillae Yue	Dec. Bupleuri			
Variation I: energetic factors determining the course	Lack of xue and defensive-qi: more prone to phase 1	Additional ventus: even acuter calor	Weakness of orthopathy (qi): faster transition into phase 4	Lack of qi worsens the course, as P und L are qi-dependent	Mare xue: part of hepatic yin, therefore worse, if xue deficient	Yin (body substance) is decisive
Variation II: „outside-inside hopping" or „inside-outside-hopping"	If yin is extremely weak: direct transition into stage 6 possible	If lack of qi and depletion of the Centr : direct transition into stage 4	If lack of qi and xue: direct transition into stage 5	"sinu-bronchitic syndrome" (transition from stage 4 to stage 2)	stage 5 may go over into stage 3, i.e. as a form of recovery in pneumonia in the elderls	In stage of recovery: i.e.still aching limbs of algor kind (1. stage)
Variation III: add. ventus	All phases tend to show more signs of yang, repletion and especially more CALOR!!					

(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

As in hypertension ventus may be involved, more calor is generated. So as we can see below the pathophysiology of calor, it explains a lot regarding symptoms and mechanisms involved in hypertension.

Again(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

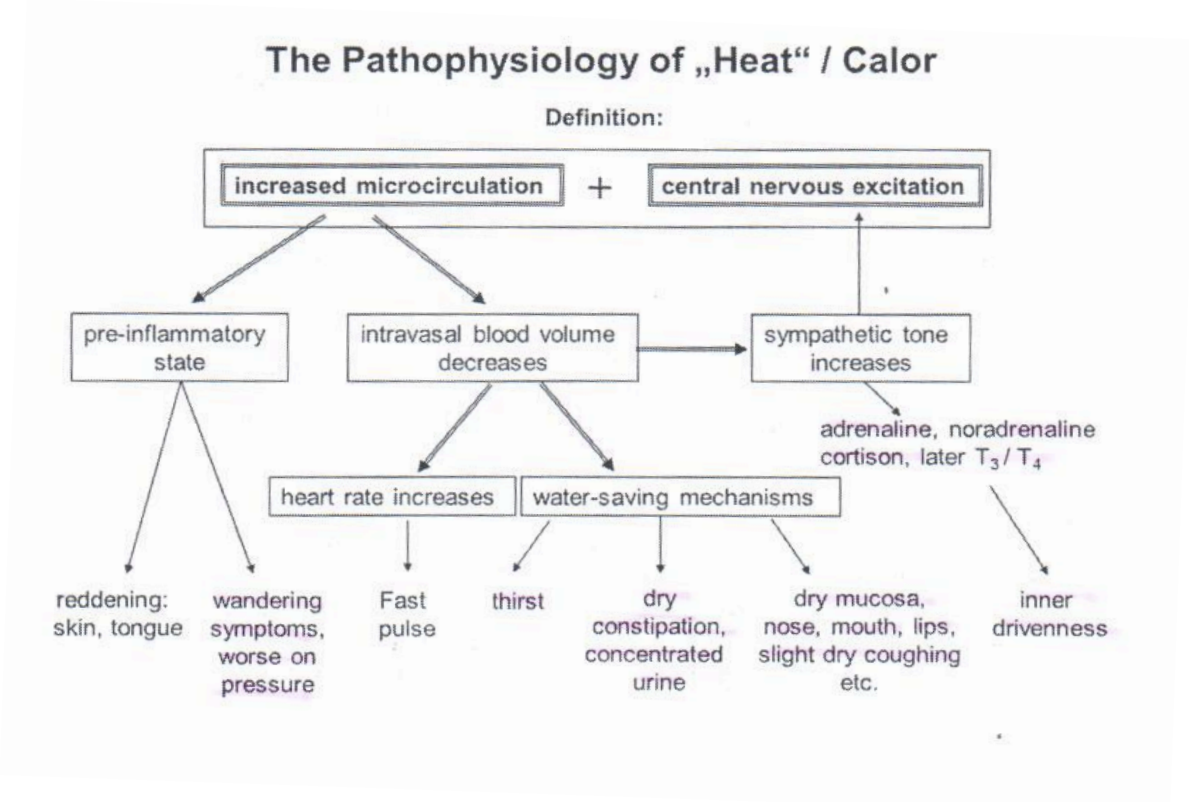


Figure 15-Pathophysiology of Calor

(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed)

Again:

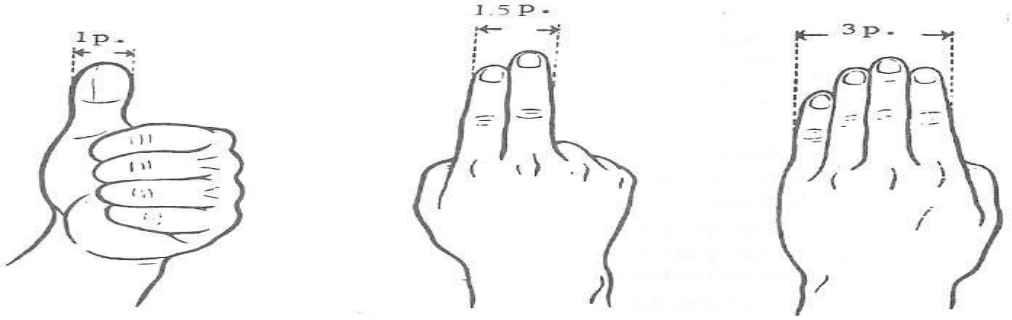
BP= CO X PR and CO= HR X SV

Therefore if calor increases the HR, stimulates the water saving mechanisms and increases sympathetic tone- thus increasing the peripheral resistance, we have here alone a good explanation for the hypertension following calor (induced by ventus). But we also have xue stagnation, which can be a consequence of qi deficiency, humor/pituita causing blockages, yin deficiency (leading to more uprising yang).

Distance Measurements in acupuncture:

The measurements in acupuncture, as everything in Chinese medicine, are done taking in account the individuality of the person being treated, therefore, when measurement of distances on the body surface are required, it must be adjusted proportionally to the patient size. Thus, the individual specific standard of proportion is the **cun.** See figure below:

Figure 16- Distance Measurement in Acupuncture



1 Cun | 1,5 Cun | 3 Cun

Commonly used acupoints for the treatment of hypertension:

An overview of previous studies showed some of the commonly used acupoints for hypertension(Flachskampf, et al., 2007)(Zhang R. H., 2007)(Macklin, et al., 2006)(Zhou & Longhurst, Neuroendocrine mechanisms of Acupuncture in the Treatment of Hypertension, 2012)(Yin, et al., 2007)(Lee, Kim, Park, Kim, Lee, & Park, 2009)

Point	Name	Chinese name	Location
V11	Radius magnus	Dazhu	1,5 cun lateral to midline at the level of protrusion of 1st thoracic vertebrae

Effects of V11:

The "crossroads" meeting point of It, Tk, F conduit and Rg sinarteria.

Dispels ventus, cools calor.

Master point of the bones. Influence on R orb, strengthen R orb.

Point	Name	Chinese name	Location
V18	Inductorium hepaticum	Ganshu	1,5 cun lateral to processus spinosus of the 9th thoracic vertebrae

Effects of V18:

Shu (dorsal inductory) point of the hepatic orb.

Strengthens the hepatic and felleal orbs, refrigerating and draining humid calor, harmonizing the qi.

Point	Name	Chinese name	Location
V23	Inductorium renale	Shenshu	1,5 cun laterally to the 2nd lumbar vertebrae

Effects of V23:

Shu (dorsal inductory) point of the renal orb

Strengthens and harmonizes the renal orb, nourishes the renal yin, tonifies the renal qi and yang

Strengthens the loins, improves the hearing and benefits ears and eyes.

Point	Name	Chinese name	Location	Neuroanathomic basis
S36	Vicus tertius pedis	Zusanli	3 cun below lower border of the patella, 1cun from the front edge of the tibia, on the fibular side, at the level of the tibia tuberosity	Subcutaneous nerve: saphenous nerve, peroneal superficial nerve Deep layer: Deep peroneal nerve

Effects of S36:

Conjunctorium of the Stomach conduit- Earth point on Earth conduit.

Regulates the relation between the vegetative capacity to function (QI) and the functional capacity bond to the body fluids (XUE)

Eu-regulation: stabilizes the Centre (S and L orb)

Acts in all forms of hidrostasis *Humor*

Point	Name	Chinese name	Location	Neuroanathomic basis
S40	Abundantia	Fenglong	Exactly 8 cun equidistant from the lower border of the patella, S35 and the prominence of the external malleolus 1cun lateral to S38	Subcutaneous nerve: saphenous nerve, superficial peroneal nerve Deep layer: deep peroneal nerve

Effects of S40

Nexorium where the link of the stomach conduit to lineal conduit originates

Acts in ventus symptoms

Transforms humor and pituita

Calming effect, bringing down the yang (reduces function)

Point	Name	Chinese name	Location
IC4	Valles coniunctae	Hegu	Depression on the radial side of the index finger, distal to the 2nd metacarpophalangeal joint, on the border of red and white flesh

Effects of IC4:

Point f qi originale.

Dispels ventus.

Command point of face and mouth.

Liberates extima.

Promotes labor

Point	Name	Chinese name	Location	Neuroanathomic basis
IC11	Stagnum curvum	Quchi	Arm flexed at elbow - this point is in the depression midway between the lateral epicondicondyle of the umerus and the transverse crease of the elbow	Subcutaneous nerve: ante brachial dorsal cutaneous nerve Deep Layer: Radial nerve trunk

Effects of IC11:

Conjuntorium of the crassintestinal conduit-Earth point in a Metal conduit-promotes the yin and Orthopathy

Promotes the yin of the conduit, which is responsible for the rhythm and enteral coordination e acts in metal phase (relaxation), eu regulation to metal phase

Dispels ventus-relaxing action on sympathetic system

Cools calor balancing the building energy and xue

Point	Name	Chinese name	Location	Neuroanathomic basis
F20	Stagnum venti	Fengchi	Depression between the sternocleidomastoid and trapezius muscles, at the same level as Rg 16	Depression between the sternocleidomastoid and trapezius muscles

Effects of F20:

Meeting point with the Tk conduit, yang wei mai, yang qiao mai (active in uprising yang)

As the name says 'pool of wind', means point where the disturbance of flow is localized.

Major point of ventus disorders- Dispels ventus

Point	Name	Chinese name	Location
F34	Fons tumuli yang	Yanglingquan	Depression anterior to the head of the fibula

Effects of f34:

Conjunctorium of the felleal conduit. Earth point on a wood conduit.

Strengthen the qi in the middle and lower caloric, thus stabilizing and regulating the lineal and renal orb, but also the hepatic and the felleal orb-benefiting the tendon and joints, eliminating humor, ventus and calor heteropathies.

Point	Name	Chinese name	Location	Neuroanathomic basis
F39	Campana suspensa	Xuan zhong	3 cun above external malleolus	Anterior border of the fibula

Effects of F39:

Connects all three yang channels of the foot (felleal, Vesical and Stomach)

Powerfully deploys qi in middle and upper caloric, thus dispels ventus, control the yang, transforms pituita, draining humor.

Promotes the smooth flow of hepatic and felleal qi.

Master of the marrow.

Point	Name	Chinese name	Location	Neuroanathomic basis
L4	Basis metatarsalis	Gongsun	1 cun proximal to to L3, in a depression, distal to the basis of 1st metatarsal, on the border of the red and white flesh	Subcutaneous nerve: saphenous nerve, superficial peroneal nerve Deep layer: medial plantar nerve

Effects of L4:

Nexorium linking Stomach and Lienal conduits. Strengthens the Stomach and Lienal Orb

Opens the synarteria Impedimentalis

Corrects repletion caused by humor

Regulates qi and transforms excessive humor

Calms shen

Point	Name	Chinese name	Location	Neuroanathomic basis
L6	Copulatio trium yin	Sanyinjiao	3cun vertically above the medial malleolus, at the posterior margin of the tibia	Subcutaneous nerve: saphenous nerve Deep layer: tibial nerve

Effects of L6:

Connects all 3 yin conduits of the leg (Lienal, Renal and Hepatic).

Strengthens the Lienal orb, improving the metabolism.

Relaxes the hepatic orb and stabilizes the Renal orb, makes more dynamic and enhance fluids circulation. Master of the lower caloric.

Point	Name	Chinese name	Location
L9	Fons tumuli yin	yinlingquan	With the knee flexed, it is in a depression at the lower border of the medial condyle.

Effects of L9:

Conjunctory of the lineal conduit. Water point on an earth conduit.

Regulates the lineal orb, transforms humor.

Local point for the knees.

Point	Name	Chinese name	Location
H2	Intertitium ambulatorium	Xingjian	Between 1st and 2nd toe, distal to the terminal phalanx of the big toe

Effects of H2:

Effusory of the hepatic conduit (Fire point on a wood conduit)

Stabilizes and harmonizes the hepatic orb.

Cools calor.

Point	Name	Chinese name	Location	Neuroanathomic basis
H3	Impedimentale major	Taichong	Between the metatarsals of the 1st and 2nd toe, in a depression about 1,5 cun proximal to the terminal phalanx of the big toe	Subcutaneous nerve: nerve saphenous superficial

Effects of H3:

Proven action in conventional medicine: increases the plasmatic level of endothelin, ameliorates hypertension

In TCM: Inductorium of the hepatic conduit-Earth point (orthopathy) on a wood conduit-potential, i.e. brings eu-regulation to the potential

Point of hepatic qi originale

Stabilizes and regulates hepatic and felleal orb, regulating and reducing the excess activity of Xue

Point	Name	Chinese name	Location	Neuroanathomic basis
Pc5	Foramen intermedium	Jianshi	3cun proximal to the transverse crease of the wrist, between tendons of the Palmaris longus and the flexor carpi radialis	Deep layer: deep median nerve

Effects of Pc5:

Transitory of the Pc conduit. Metal point on fire conduit.

Calms the shen and cardial orb.

Stabilizes and regulates the C and Pc orbs, calming ventus, checking calor

Directs qi down to the middle caloric

Transform pituita and harmonize the S orb.

Point	Name	Chinese name	Location	Neuroanathomic basis
Pc6	Clusa interna	Neiguan	2cun proximal to the transverse crease of the wrist, between tendons of the Palmaris longus and the flexor carpi radialis	Deep layer: deep median nerve

Effects of Pc6:

Nexory of pericardial conduit

Opens the synarteria retinens yin

Stabilizes and harmonizes the cardial and lineal orb, regulation qi, draining and dispersing Yang and ventus, calor and humor

Point	Name	Chinese name	Location	Neuroanathomic basis
C7	Porta shen	Shenmen	Proximal and radial to pisiform bone in the transverse crease of the wrist, radial to the flexor carpi ulnaris	Subcutaneous nerve: radial cutaneous nerve Deep layer: ulnar nerve trunk

Effects of C7:

Inductorium of cardial conduit: 3rd antique point

Earth point (eu-regulation)of the cardiac conduit

Stabilizes the cardial orb (which transforms potential into function

Re-establishes the functional capacity of the sinarterias e regulates the yang excess function)

Point	Name	Chinese name	Location
R3	Rivulus maior	Taixi	Midway between the medial malleolus and the Achilles tendon (palpable pulse)

Effects of R3:

Indutorium of the renal conduit (qi original point) Earth point on a water conduit.

Stabilizes and regulates the renal and hepatic qi. Cools calor

Point	Name	Chinese name	Location	Neuroanathomic basis
R7	Amnis recurrens	Fuliu	In a depression at the anterior margin of the Achilles tendon, 2 cun above R3	Subcutaneous nerve:saphenous nerve, sural medial cutaneous nerve Deep layer: tibial nerve

Effects of R7:

It's is the point for the fluids, regulate the corporal fluids e promotes renal yin (promotes the regeneration)

It is the transitory of the renal conduit-metal point on a water conduit-stimulates the distribution of the vegetative capacity to function (qi)on the conduit, with protective effects.

Stabilizes and regulates the fluid metabolism, controlling specially the calor-humidity

Point	Name	Chinese name	Location	Neuroanathomic basis
Rg 14	Omnium defatigatorum	Dazhui	Depression below the 7th cervical vertebra	Below 7th cervical vertebra

Effects of Rg 14:

"Foramen of all stress and strain"

Stabilizes and regulates the qi of the centre , thus transforming calor humidus.

Dispels ventus, cools calor

Calms shen and ventus internus

Strengthens the qi and yang in deficiency conditions

Strengthens the hepatic and pulmonary orb

Point	Name	Chinese name	Location	Neuroanathomic basis
Rg 20	Conventus omnium	Baihui	In the centre of the top of the skull, aprox. 7cun from the posterior and 5 cun from the anterior hairline.	At the junction of a line connecting the apices of the ears and the midline.

Effects of Rg 20:

Meeting point of yang conduits (F, V, Tk) and hepatic conduit.

Calm ventus, pacify yang, calms the shen.

Stabilizes and regulates the hepatic orb.

Point	Name	Chinese name	Location
Rs 4	Prima clusarum	Guanyuan	3 cun below the navel

Effects of Rs4:

Mu point of tenuintestinal Insertion poit of the Rs,hepatic and lineal conduits

Stabilize the renal orb, consolidating the original qi

Controls and directs the yang downwards.

Point	Name	Chinese name	Location
Rs 6	Mare qi	Qihai	1,5 cun below the navel

Effects of Rs6:

Tonifies the qi.

Stabilizes and regulates the renal orb.

Directs the yang downwards.

Point	Name	Chinese name	Location
Rs 12	Conquisitorium stomachi	Zhongwan	4cun above the navel and 4 cun below xiphoid process

Effects of Rs 12:

Mu point of stomach.

Point of reunion of the functions of all yang orbs.

Regulates the stomach orb, harmonizing its qi, -thus strengthening the centre, draining humor

Point	Name	Chinese name	Location
Ex-HN-5	Taiyang	Taiyang	Depression in 1cun lateral to the mid point of a line connecting the lateral extremity of the eyebrow and the outer canthus of the eye.

Effects of the taiyang:

Dispels ventus,Cools calor.

Transforms humor.

(Greten H. , Understand TCM Scientific Chinese Medicine- The heidelberg Model, 2010 5th ed),(Zhang R. H., 2007)(Jin, 2006; Kaptchuk, 2002)(Porkert M. a., 1995)(Hempen, 2006)(Zhou & Longhurst, Neuroendocrine mechanisms of Acupuncture in the Treatment of Hypertension, 2012)(Stéphan, 2010)(Xia)(Focks, 2008)(Deadman, Al-Khafaji, & Baker, 1998)(Ferner & Staubesand, 1984)

CLINICAL RESEARCH PROTOCOL

II. CLINICAL RESEARCH PROTOCOL

Title: Effect of Acupuncture as a complementary therapy in the treatment of patients with Essential Systemic Hypertension

1.Background:

Hypertension prevalence worldwide is estimated to be almost 1 billion individuals and it can be related to as much as 7million deaths per year. Moreover, it is the first cause of death worldwide. It is estimated that in Portugal about 42% of the adult population aged 18-90 years has hypertension. That number corresponds to approximately 3 million people. Among those patients only 36% are aware of their high blood pressure and only about 11% are treated adequately. The prevalence of hypertension increases with the age of the people, reaching about 78% in older than 64 years.(Macedo, Lima, Silva, Alcantara, Ramalhinho, & Carmona, 2005)

In the first year of therapy only 60% of the patients will continue the medication (Caro, Speckman, Raggio, & Jackson, 1999)(Massaglia, et al., 2005)and after 5-10 years as much as 60% will abandon their prescription for hypertension(Caro, Speckman, Raggio, & Jackson, 1999; Chao, Shen, Tjen-A-Looi, Pitsillides, Li, & Longhurst, 1999).

The use of acupuncture could help overcome these difficulties, by either diminishing or substituting the amount of drug required, and also because with frequent visits to the clinic it eases the compliance to the treatment (drugs and/or adjustment of lifestyle).

2. Research team

2.1 Main investigator:

2.1.1 Deise Noriko Matsui Nishimura

- Physician graduated from Faculdade de Medicina da Universidade de São Paulo (USP) – Brazil, and degree recognized by Faculdade de Ciências Médicas da Universidade Nova de Lisboa
- Specialized in Cardiology (3 years of internship) at Instituto do Coração (INCOR)- do Hospital das Clínicas da FMUSP
- Master student of Traditional Chinese Medicine at the Instituto de Ciências Biomédicas Abel Salazar (ICBAS)

2.2. Research supervisors

2.2.1 Main supervisor:

Prof. Dr. Henry Johannes Greten

- Head of the Heidelberg School of Traditional Chinese Medicine
- President of the German Society of Traditional Chinese Medicine (DGTCM), Heidelberg-Germany
- Associated professor at ICBAS-Universidade do Porto

2.2.2 Co-supervisors:

Prof. Dr. Jorge Machado

- Associated professor at ICBAS- Universidade do Porto (UP)

Dr. Nuno Cândido Maia Correia

- Assistant physician at Hospital de São João-Porto
- Master in TCM from ICBAS-UP

3.Objectives:

3.1 **General objective**: To study the acute effect of acupuncture in patients with mild to moderate essential hypertension (EHT). We search for answers to the following questions:

1. Is there an acute effect of the treatment of hypertension?
   We plan to answer this question by measuring the BP before and after each treatment.
2. Can we consider that " white coat" hypertension is playing a role in the results?
   In order to avoid this effect we will use the comparison between the 24-ABPM before and after the course of 3 treatments.
3. Does acupuncture have an effect in the average systolic, average diastolic or both?
   We will compare the average systolic and diastolic separately.

4. Is there any period during the day in which acupuncture exerts preferentially its effects?

   We will compare the average systolic and diastolic blood pressures during daytime with night-time.

5. Does acupuncture have an effect in long term prognosis for cardiovascular events?

   We will assess the BP variability-(standard deviation around mean values).The variability of blood pressure may have a prognostic value in hypertension patients. (Mancia, et al., 2007)(Mancia, Prognostic value of long-term blood pressure variability:the evidence is growing, 2011)

4. Methods:

4.1 Setting:

The study will be performed in an outpatient clinic, in Brejos do Azeitão, Portugal.

4.2. Study population:

Patients from general population, younger than 70 years old, recruited via local newspaper, leaflets in clinics, with essential mild to moderate hypertension.

4.2.1 Inclusion Criteria:

- Patients with essential hypertension high normal, grade 1 , grade 2 according to ESH/ESC guidelines 2007 i.e. Systolic Blood Pressure (SBP) <180mmHg or Diastolic Blood Pressure (DBP) <110mmHg
- Age < 70 years old
- No change in antihypertensive medications in the last 60 days
- Patient must sign a written informed consent.
- Patients naïve to acupuncture

4.2.2 Exclusion criteria:

- Secondary causes of HT
- History of white coat hypertension

- History of stroke, coronary heart disease
- History of heart failure
- Poor compliance to the study
- Bleeding disorder
- Needle panic/fear
- Neurologic diseases affecting motor, sensorial pathways
- Mental /cognitive diseases
- Endocrinopathy (hyper/hypothyroidism, acromegaly, Cushing…)

4.3 Study design

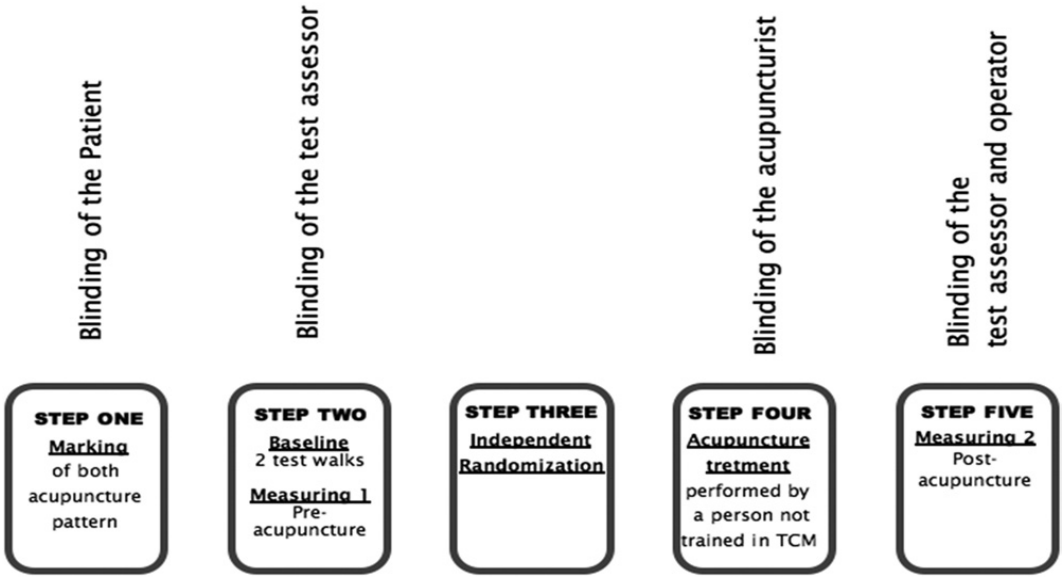
This study will be triple (patient, interventionist, data collector) blinded, randomized, controlled, prospective, pilot clinical trial.

The patients will come for 5 days during a week, from Monday to Friday (Figure 18)

4.3.1. Blinding

Blinding will be done based on the model already applied in a Heidelberg group's study, as follows:(Hauer K, 2011)

Figure 17- Blinding in the study protocol



Hauer K, Wendt I, Schwenk M, Rohr C, Oster P, Greten HJ, Arch Phys Med Rehabil 2011 Jan; 92(1): 7-14 (with permission)

- In step 1 (blinding of the patient), a trained acupuncturist will mark in 2 different colours the “real” acupoints and the sham point. The sham points will be the control patients.
- In step 2 (blinded assessor, baseline measurement), the type of intervention will be invisible to the BP pressure taking person and to the 24-ABPM analyser, resulting in blinding of the test assessors.
- In step 3 randomization to 1 of the 2 study groups
- In step 4 (blinding of the acupuncturist), a person not trained in TCM, but supervised will perform the treatment using the points marked with the respective colour according to the randomization code.
- In step 5 (post-acupuncture measurement), effects of the acupuncture will be assessed with a BP measurement analysis and after the 3 days-protocol a new 24 ABPM will be taken.

This blinding of the interventionist will take place only on the first day due to technical reasons (many points utilized in the intervention, with different techniques of stimulations). Data (HR/BP) from the first day of treatment will be compared to the baseline to check for super acute effects with triple blinded treatment.
The patient and assessors blinding will continue on the following days.
The blinding of the patients is important because their beliefs and/or expectations regarding the therapy can influence the response.(Kaptchuk, 2002)(Flaten, Simonsen, & Olsen, 1999). Because this protocol has a short interval we believe that the possibility to keep the masking will be effective-no “guessing” by the patient regarding which group he/she is, either according to the BP levels observed or by talking to each other about the colours of the points.

4.3.2. Randomization

Drawing an envelope among a pool of envelope containing different colours will randomize subjects into 2 groups: real or sham acupuncture.

4.3.3. Control

Control will be done in an invasive control regimen, using acupoints outside the conduits, based on a previous publication in Circulation(Flachskampf, et al., 2007), plus points without known autonomic effects or with no effects

on experimental hypertension (Zhou & Longhurst, Neuroendocrine mechanisms of Acupuncture in the Treatment of Hypertension, 2012), or without indication to hypertension according to TCM

4.3.4 Experimental protocol

4.3.4.1. Monday-Day 0 "Baseline" or pre-intervention phase

The study personnel will explain to the subjects details about the study, the number of days required, the acupuncture treatment (penetrating, thin needles) and possible but minimal risks of acupuncture treatment (hematoma, infection, fainting etc.). The signature of the written consent (see appendix 2) will be obtained, BP/HR measured and the installation of the 24-ABPM will be done.

4.3.4.2 Tuesday –Randomization and triple blinded study

The patients will come to the clinic to take out the 24-ABPM and then will get the points marked in 2 different colours by an acupuncturist. Then the BP and HR will be measured according to ESH/ESC guidelines.

After this procedure, they will draw the envelope containing the colour of the group assigned and will proceed to the supervised nurse, who will puncture the points marked with the same colour contained inside the envelope. (The patient must not show the colour to any other person). After 30min of the treatment a person other than the nurse who applied the puncture will assess the BP and HR again.

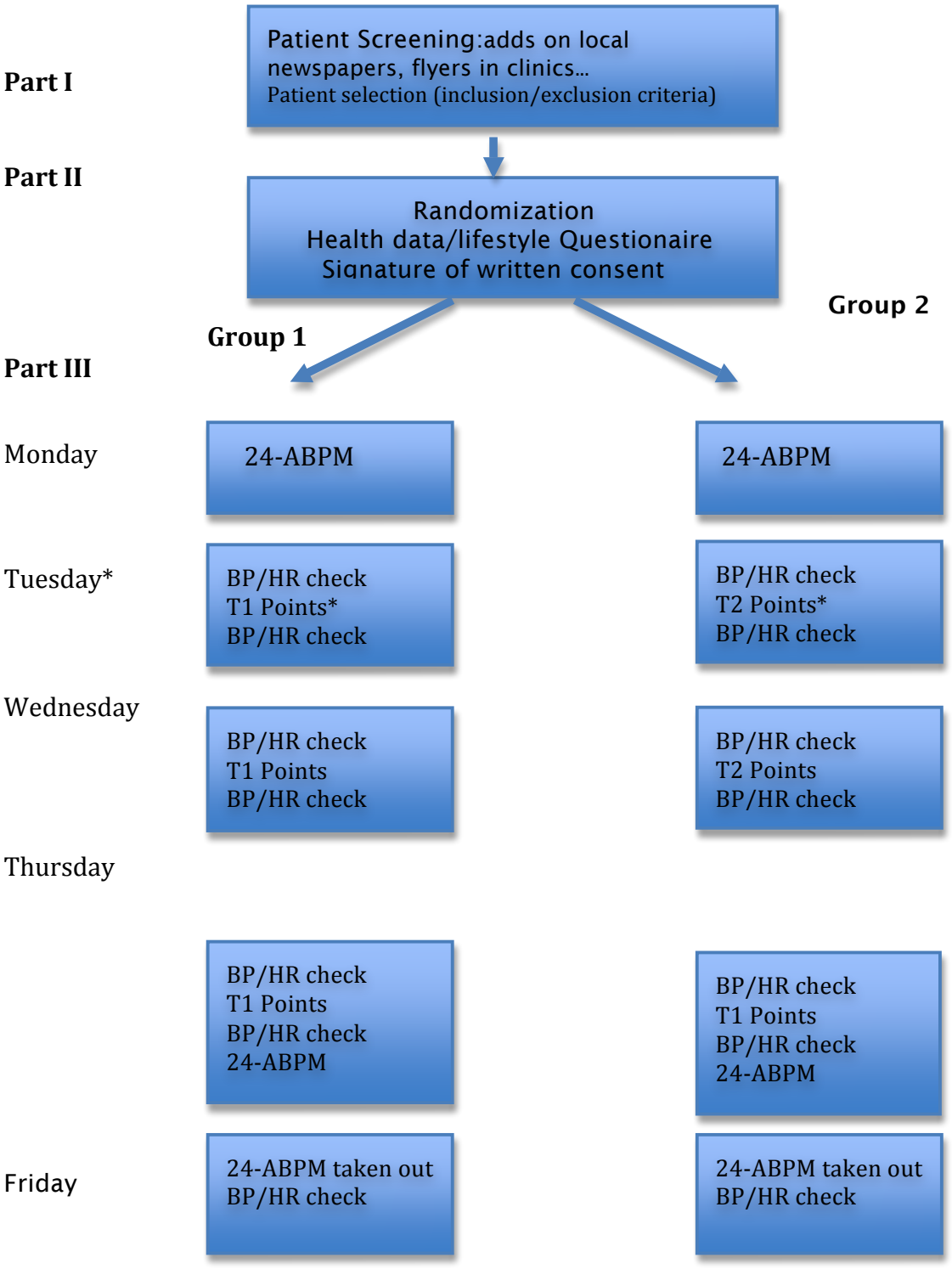
4.3.4.3 Wednesday and Thursday

Patients will return to the clinic and have their BP and HR checked before and after 30 min of the intervention. In these days a certified acupuncturist will do the intervention (who will now be allowed to see the colour group the patient is, but the remaining personnel shouldn't know the colour until the end of the study protocol). After the intervention on Thursday the 24-ABPM will be installed again.

4.3.4.4 Friday

Take off the monitor. BP and HR checked. Data will be analysed by a third person unaware of the protocol.

Figure 18 - STUDY DESIGN



- Treatment on Tuesday will be done by blinded acupuncturist (see above) Group 1 = 'real acupuncture" Group 2 =sham acupuncture (control)

Part IV: Data analysis (independent analyser): average systolic and diastolic BP, analysis of the average day-time and night time systolic and diastolic BP BP variability analysis

4.4 Intervention:

Acupuncture 3 sessions (1session/day) on Tuesday, Wednesday and Thursday .

BP and HR measurement before and after the acupuncture sessions

BP to be measured according to ESH/ESC recommendations- see above

24-ABPM before and after the treatment period

Acupuncture treatments:

- **Group 1:** "real" acupuncture- based on a concept of acupuncture according to Heidelberg Model of Chinese Medicine, aiming close to the principle of ALT and suitable for yin deficiency and uprising yang
  - F39 –Felleal (Gall Bladder)39: campana suspensa/Xuan zhong
  - Rg14- Regens (GV)14: Omnium defatigatorum/ Dazhui
  - Pc 6- Clusa interna/ Neiguan
  - F20- Felleal (Gallbladder) 20: Stagnum venti/Fengchi
  - Rs12- Respondens 12:conquisitorium stomachii/Zhongwan
  - L6- Lienal (Spleen) 6: Copulatio trium yin/Shangqiu
  - R7: Renal (kidney) 7: Amnis recurrens/Fuliu

- **Group 2:** sham-acupuncture- an invasive control using acupoints outside the conduits, based on a previous publication in Circulation(Flachskampf, et al., 2007), plus points located outside the conduits between points without known autonomic effects or with no effects on experimental hypertension (Zhou & Longhurst, Neuroendocrine mechanisms of Acupuncture in the Treatment of Hypertension, 2012)

  Both treatments will be performed using the same number of needles, applied bilaterally (except Rg14 and Rs12, because they are in the midline), needles will be left for 30 minutes, in a calm and tranquil treatment room in the clinic.

  Stainless steel sterile, single use needles with ø=0,25mm and length of 25mm will be used in both groups.

4.5 Main parameters:

Blood pressure measurements:

Should be done as the ESH/ESC recommendations(ESH/ESC, 2007):

- Patients should rest for several minutes in a quiet room before measurement
- At least 2 measurement with interval of 1-2 minutes, and more if those 2 are very different
- The bladder should be adequate to the arm size
- Keep the cuff ate heart level
- Use phase I of Korotkoff sound for systolic BP and phase V (disappearance) for the diastolic BP
- Measure the BP at both arms to detect possible difference as a consequence of peripheral arterial disease. Use the higher value as a reference value
- Measure BP 1 and 5 min after orthostatic position in elderly, diabetics and other conditions necessary to verify postural hypotension
- Measure the heart rate after the second measurement in the sitting position (pulse palpation for at least 30 seconds).

24h-ABPM

The 24h ABPM was chosen as an assessment tool because it has some advantages over the office only measure:

- Provides the average blood pressure, as well as a mean values over a period of time (day, night, morning)
- Reflects the variation of BP during daily life, not only during office visits
- Absent or negligible “white coat” or placebo effect(Staessen, et al., 1994)(Mancia, Omboni, Parati, Ravogli, Vilani, & Zanchetti, Lack of placebo effect on ambulatory blood pressure, 1995)
- Better prognostic value
- Gives information about BP variability (standard deviation around mean values)

- And very importantly for a study protocol- it has a higher reproducibility over time(Coats, Radaelli, Clark, Conway, & Sleight, 1992)(Mancia, Ulian, Parati, & Trazzi, 1994)

Data to be analysed:

1. 24 hour-Ambulatory blood pressure monitor (ABPM)- average systolic and diastolic BP- before and after the treatment regimen
2. Regular blood pressure BP/HR checking before and after each session.
3. Analysis of the average day-time and night time systolic BP and diastolic BP –before and after treatment regimen
4. Analysis of the BP variability and by analysing this parameter we could assess indirectly the effect of acupuncture also in the evolution of worsening hypertension target organ lesion and incidence of cardiovascular events.(Mancia, Prognostic value of long-term blood pressure variability:the evidence is growing, 2011)(Mancia, Omboni, Ravogli, Parati, & Zanchetti, 1995)

5. Study steps plan:

1st step- ICBAS ethics committee approval

2nd step- publishing in local newspaper, flyers in local health care out patient clinics

3rdstep- patient selection

4th step- study protocol

5th step- Publication

6. Research partnership:

ICBAS TCM Master Programme.

7. Ethical considerations:

This research protocol has been submitted to the Ethics Committee (EC) of ICBAS for approval. (Appendix 1)

The study is to be conducted according to the 1964 Helsinki Declaration and international standards of Good Clinical Practice requirements.(ICHS, 1997)(Medical Research Council , 1998)

All subjects for this study will receive a consent form describing the protocol and offering sufficient information for them to make an informed decision about their participation in this study. Subjects are informed about the goals, methods, expected benefits, and potential risks or discomforts, and have the right to decide to withdraw or continue at any moment during his/her participation; subject is also aware that no prejudice will result if him/her refuses to participate or withdraws from the study. (Appendix2)

This informed consent is to be obtained from all participants before randomization and is considered an inclusion criteria. This consent form is to be approved by the ethic committee and must be signed by the subject or legally acceptable surrogate and the research professional obtaining the consent.

Multiple studies have shown that the incidence of adverse effects of acupuncture is low. (Melchart, et al., 2004)(Witt, 2011)(Ernst, Strzyz, & Hagmeister, 2003)(Norheim, 1996)

Subjects will be asked about adverse experiences at each visit, defined as any unfavourable and unintended sign, symptom or disease temporally associated with the use of the acupuncture treatments.

The trial will be stopped if the investigators believe there is an unacceptable risk of serious adverse events in one of the treatment arms.

8. Results:

This proposed clinical protocol has been submitted for approval by the Ethics Committee of ICBAS (appendix 1), the authorization to work on the clinic has been granted (appendix 3), and steps towards its completion are being accomplished.

Results of this trial may provide data regarding acute effects of acupuncture for hypertension that could be useful for researches with larger population, longer follow up periods.

Since there is no data yet available at the time of this thesis submission, we can only comment on the study hypothesis.

The 2 groups should be with no statistically significant differences regarding age, gender, use of medication

It is expected that the real acupuncture could show decrease in blood pressure even after one treatment and this effect could be assessed with the BP measurement before and after each session.

It is foreseen that the real acupuncture could demonstrate a significant reduction both in the mean systolic and mean diastolic BP during the 24-ABPM, compared to the sham group.

Also it is anticipated that the variability of the BP will increase significantly more in the real acupuncture group, thus giving the indication that it can also reduce the cardiovascular events in the future.

9. Discussion

This study may reveal a significant decrease in both systolic and diastolic blood pressure, compared to the sham group because acupuncture exerts sympatholytic, pro-vagotonic, anti-inflammatory and also action on the renin, angiotensin aldosterone system, according to recent literature. Also it was discovered a specific neurological pathway participating in acupuncture inhibition of excitatory cardiovascular reflexes: a long loop pathway for cardiovascular modulation, involving the arcuate nucleus of the hypothalamus, ventrolateral periarqueductal gray, the rostral ventrolateral medulla cardiovascular centre and the nucleus raphé through direct or indirect actions, apparently acting acts through opioids (endorphins, enkephalins, perhaps endomorphin, but not dynorphin) serotonin, GABA. These entire systems have effects on the pathophysiology of the hypertension.

By analysing the 24-ABPM data we could get more accurate, reproducible measurement of the extent of the reduction induced by the treatment, in addition, it can provide information regarding to in which part of the 24 hours (day or night) the results were more pronounced.

Because it is a short time study, action of external factors such as change in medicaments, change of lifestyle, diet, alcohol intake, smoking status are less likely to happen and influence results.

This protocol results will provide data to grant a larger prospective, controlled, multi-blinded, randomized protocols, with longer follow up periods.

Limitations:

When a nurse with no knowledge of TCM applies the treatment she/he will not be able to orient the patient to ‘de-qi’, there will be no needle stimulation, which in some cases can diminish the effect of the acupuncture. There are some

points that require a specific kind of stimulation and this cannot be done without some knowledge of TCM. The following days an acupuncturist will perform the treatment.

The blinding of the interventionist will be made only on the first day due to technical reasons – a large number of points (12 in total) for a non-experienced nurse to apply. But there are reports that the utilization of some points alone can produce effects in lowering the blood pressure, such as F39.(Wei, 2006), so we could expect some results even on the first day. And the number of points will be limited to the same number of points as the sham treatment (in order to keep the blinding of the patient).

Although in this study we will utilize acupoints selected by a very well experienced Chinese and western medicine doctor, we will use the same points for a western diagnosis of hypertension, not necessarily the same Chinese diagnosis.

In this study we will include patients taking their medication, however, because this protocol is short, changes that could be attributable to change in medication are easier to avoid

The analysis of the BP variability can indirectly provide information regarding prognosis of a cardiac event(Mancia, Prognostic value of long-term blood pressure variability:the evidence is growing, 2011), this study will show it only over a short period of action of the acupuncture, longer treatment plan and follow up are necessary to confirm this information.

10. Future perspectives:

Acupuncture and TCM have existed for thousands of years and the interest in its utilization has been increasing in western world.

Although limitations exist regarding the study design, proper blinding, choosing the correct control group such as cross over design, ideal sham treatment (acupoints/nonacupoints, non penetrating needles), scientific evidences towards its usefulness is growing. And there have been more and more well designed, randomized studies with Chinese medicine/acupuncture also in the western society.

As for acupuncture to treat cardiovascular diseases, despite many research involving animals and humans, only a part of its mechanisms is known. Promising results from well-designed clinical trials suggests that it has clinical value. But there are yet a lot of unanswered questions, some of them are addressed below:

1. *Is there a specific hypertension patient group in which the acupuncture is more indicated?*
2. *Is the acupuncture efficient to substitute medicaments?*

   More studies are required to check the effects of acupuncture as a 'substitute' for the drugs prescribed, or if it is an important tool but only as a complementary therapy.

   In order to answer these questions above it would be necessary but difficult to study patients with higher grades of Hypertension and take out their medication due to ethical reasons.
3. *Is the treatment according to Chinese diagnosis superior to standard pre determined points?*
4. *Is there a specific Chinese diagnosis group in which the effect is more pronounced?*

   It makes sense to make a study design with experienced Chinese medicine doctors making Chinese diagnosis and treating using individualized treatments to check the effects when applying Chinese diagnosis individually. There were, indeed, some good studies using Chinese diagnosis, (Flachskampf, et al., 2007)(Yin, et al., 2007)(Macklin, et al., 2006), but they didn't mention the diagnosis made, and hadn't separated the groups according to their Chinese diagnosis, so it wasn't possible to know if a specific type of hypertension according to Chinese diagnosis were more "treatable" with acupuncture than the others.

A large study dividing and describing the groups according to their Chinese diagnosis would allow better correlation between western and Chinese diagnosis thus making possible to identify the groups and results.

5. *Which is the ideal duration/interval for treatment?*
6. *Is there any residual effect and if so, how long does it last?*
   Studies with longer period of treatment and follow up are required to answer these questions.
5. *Is electro acupuncture superior to manual acupuncture in the treatment of hypertension?*
   The direct comparison with proper blinding between manual acupuncture and electro acupuncture is difficult. Although there are some studies in animals, it is hard to blind the patient to these different techniques as the stimulus of the electro acupuncture can easily be identified. One option could be cross over studies, where each subject would go through all the 3 treatments, but even so an expectation of the result could influence the results. In addition, more data would be necessary to proper define the wash out period.

6. *Can the acupuncture influence the prognosis of hypertension by reducing the cardiovascular events (stroke, coronary heart disease, and heart failure?*
   Large, randomized, prospective, controlled, blinded with longer follow up not only to assess this effect indirectly by reducing the BP levels, but proper long follow up are important to check the real direct impact of acupuncture in these outcomes.

Furthermore, there are other tools in TCM that could be useful in treating hypertension and other cardiovascular diseases such as Qi Gong, phytotherapy that could also be explored and studied systematically.

Beside the difficulties, efforts towards the integration between the western and eastern medicine are worthy as it would greatly contribute to reach the ultimate goal that is to control this awful disease responsible for a great number of disabilities and deaths worldwide.

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ANNEXES